American Heart Journal

An international publication for the study of the circulation

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JULY 1967

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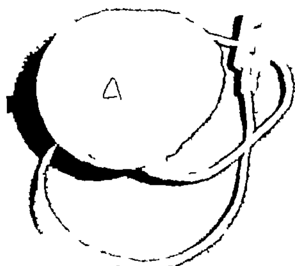
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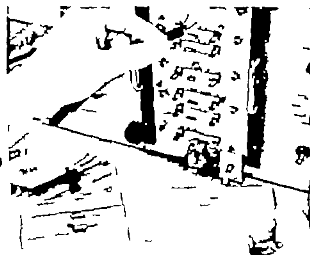
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Serial Numbers On MEDTRONIC Pacemakers Began with the First Dog Model

This is pacemaker unit #4 manufactured in 1960 for experimental implantation in a dog. Note how the serial number has been scratched into the silicone surface. Medtronic has assigned serial numbers chronologically ever since it began manufacturing electronic medical devices.



The electronic components necessary to form an individual pacemaker are mounted in a "test jig" to determine the unit's functional parameters which are recorded on a quality control card that accompanies the unit throughout production. These parameters are rechecked many times during the manufacturing procedure. The quality control card carries the serial number of the completed unit.

Placing serial numbers on manufactured devices always has been a manufacturing necessity at Medtronic. Beginning with the first implantable pacemaker manufactured for laboratory experimentation with a dog, all Medtronic devices have been individually identified. For example, before a pacemaker is assembled, its components are brought together to form a "breadboarded" pacemaker and the unit is given a serial number. Cardiac electrodes also are independently serial numbered.

An important factor in progress is the lesson of history. To be useful, history must be documented and analyzed. Because of rapid evolution, a manufacturer of electronic devices must properly identify the materials and the manufacturing procedures involved in order to make analysis possible. Each Medtronic unit carries a detailed history which begins with lot numbers of individual components at time of manufacture and ends with analysis of the unit after its retirement from service.

An analysis of the service history of Medtronic pacemakers is periodically distributed to the medical profession. These analysis records enable Medtronic to state a pacemaker reliability factor which is based on actual experience.

Serial numbering is only one of many practices in the extensive quality control and reliability assurance programs conducted by Medtronic. The depth of these quality control and reliability assurance programs can be fully appreciated only through a tour of the plant. You will see that Medtronic does everything possible to better serve you and your patient.



Medtronic, Inc.

3055 HIGHWAY EIGHT MINNEAPOLIS, MINNESOTA 55418
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THE THERAPEUTIC RESPONSE YOU NEED

WITH THE DIURETIC YOU KNOW

DIURIL®
CHLOROTHIAZIDE



Edema; hypertension.

Contraindications: Anuria. Increasing azotemia and oliguria. Known sensitivity to this compound. Nursing mothers.

Warnings: May precipitate or increase azotemia. Use cautiously in impaired renal function to avoid cumulative or toxic effects. Minor alterations of fluid and electrolyte balance may precipitate coma in hepatic cirrhosis. Dosage of other antihypertensive drugs, especially ganglion blockers, must be reduced by at least 50 percent because DIURIL potentiates their action. A further reduction in dosage or even discontinuation of the other antihypertensive drugs may be necessary as blood pressure falls. Stenosis and ulceration of the small bowel causing obstruction, hemorrhage, and perforation have been reported with the use of enteric-coated potassium tablets, either alone or with nonenteric-coated thiazides. Surgery frequently required and deaths have occurred. Such formulations should be used only when indicated and when dietary supplementation is impractical. Discontinue immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported for sulfonamide derivatives, including thiazides. When used with other antihypertensive drugs, careful observation for changes in blood pressure must be made, especially during initial therapy. Since thiazides appear in breast milk, use is contraindicated in nursing mothers. Thiazides cross placenta and appear in cord blood. In women of child-bearing age, potential benefits should be weighed against possible hazards to fetus.

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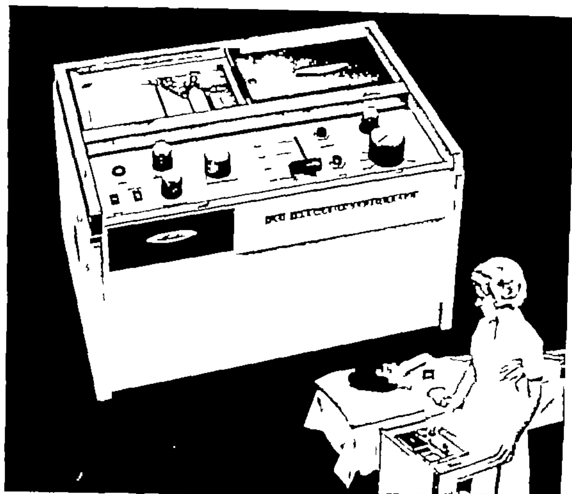
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WHERE TODAY'S THEORY IS TOMORROW'S THERAPY

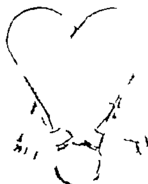
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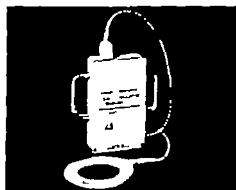
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Schwartz Medtronic CSN Stimulator

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R F pulses are received and formed to appropriate shape for nerve stimulation by this implantable receiver



Bursts of R F energy are generated and transmitted through skin from external battery powered unit Frequency and energy levels are adjustable

Medtronic R Wave Coupled Pulse Generator

MODEL 5837



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Synchronous-coupled pulse pacemaking

Demand pacemaking

• Standard pacemaking

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a built-in safety factor in digitalis therapy for geriatric patients



Elderly patients are more prone to overdigitalization and toxicity. The zone between digitalization and digitoxicity becomes narrower with advancing age.

Smooth maintenance is possible with the use of *powdered leaf digitalis*. Overdosage or intolerance with *powdered leaf digitalis* is usually signalled by anorexia, nausea and vomiting, diarrhea or visual disturbances ... a 'built-in safety factor' to help avoid serious cardiac arrhythmias. These traditional warnings are often absent when certain purified crystalline preparations are utilized.

REFERENCES: 1) Herrmann, G.R. Geriatrics 21:109, 1966. 2) Reed, R.R. and Anderson, M.W. [illegible] Lancet 86:41, 1966. 3) Dall, J.L.C. Lancet 1:194, 1965. 4) Herrmann, G.R. J.A.M.A. 191:776, 1965. 5) Dubnow, M.H. and Burchell, H.B. Ann. Int. Med. 62:956, 1965.

DOSAGE: Dosage should be carefully regulated to individual requirements of each patient. Average Oral Dose: rapid digitalization – 1.5 Gm. (22½ gr.) – 0.6 Gm. initially, followed by 0.2 Gm. every six hours until digitalization ... accomplished; slow digitalization – 0.3 Gm. daily for 3 to 7 days; maintenance – 0.1 Gm. (1½ gr.) daily.

CAUTION: Digitalis therapy should be withheld when signs of intoxication appear. Toxicity ... more frequently encountered in patients with hypokalemia, hypothyroidism, advanced hepatic or renal disease and in aged or debilitated patients. Potassium depletion, usually caused by diuretic agents, or electrolyte manipulations sensitize the heart to digitalis.

AVAILABILITY: 0.1 Gm. (1½ gr.), 60 mg. (1 gr.), [illegible] (¾ gr.) and 30 mg. (½ gr.) pills in bottles of 100.

PIL-DIGIS®

brand of
powdered leaf digitalis

also known as PIL. DIGITALIS (Davies, Rose®)

DAVIES ROSE-HOYT
Pharmaceutical Division
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Needham, Mass. 02194



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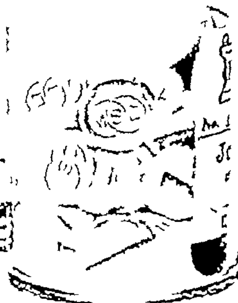
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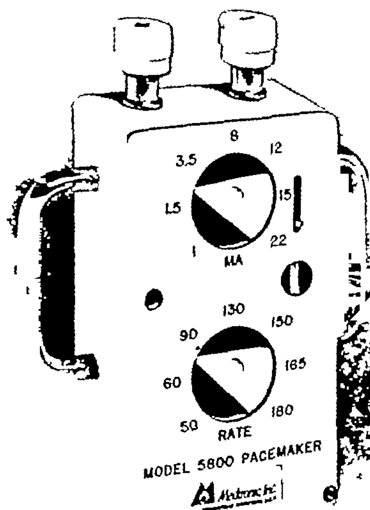
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Editorial

Myocardial infarction shock revisited

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The term "cardiogenic shock" has long been applied to the clinical syndrome of hypotension and inadequate peripheral circulation which follows acute myocardial infarction. Use of this diagnostic phrase implies that the shock associated with myocardial infarction represents a homogeneous entity which has as its origin inadequate cardiac function.

The low cardiac outputs which have been uniformly recorded in patients with myocardial infarction shock[1-3] might appear to support this unitary concept. However, a few thorns have appeared on the vine. Cardiac output is not always lower in patients with shock than in those with uncomplicated myocardial infarction. Indeed, a lesser rise in peripheral resistance has been described as the main distinguishing hemodynamic feature of the patients with shock.[4] Furthermore, a cardiac output which is at least as low as that in myocardial infarction shock is frequently observed in the shock associated with hemorrhage, sepsis, and a variety of other medical diseases. Since these forms of shock are not regarded as being "cardiogenic," the assumption must be that the mechanism of the low output in these cases is different than that after myocardial infarction.

Is inadequacy of cardiac function the feature which distinguishes myocardial infarction shock from other forms of shock? The most practical clinical means of assessing myocardial performance is to relate cardiac filling pressure to cardiac output, stroke volume, or stroke work. If atrial pressure is high and output low, it is apparent that the heart is operating on an abnormal Starling curve. When atrial pressure is low or normal, however, a low cardiac output is not necessarily indicative of heart failure. In this situation adequacy of the heart may be tested by acutely increasing cardiac filling pressure and observing whether cardiac output rises sharply (normal function curve) or whether the output response is attenuated.

Although many patients with shock after acute myocardial infarction demonstrate impaired cardiac performance, others exhibit no apparent abnormality of myocardial function at the time they are tested. In these latter patients the rapid infusion of dextran restores normal cardiac output without an abnormal elevation of right atrial pressure (Fig. 1). Since right atrial pressure rises with left atrial pressure during volume expansion, and the patients show no signs of pulmonary congestion, it is probable that this response indicates adequate left ventricular function. A beneficial response to volume expansion in myocardial infarction shock has also been recently reported by others.[12]

If patients with shock after myocardial

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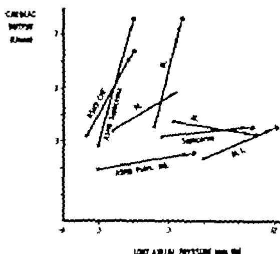


Fig. 1 Response t pid infusion of 500 ml of low molec lar weight dextran 8 patient w th shock low cardiac outpu nd normal or low right trial pressure Normal ardiac output was restored in 4 patient w thout an bnormal ele tion of trial pressure Tw of hese patient had acut myocardial infarction (M I) and 2 had severe arteriosclerotic heart disease (ASHD) The other 4 patients exhibited marked impairment of cardiac f nction nce volume expansion increased atrial pressure w thout much of rise n cardiac output Two of these latter patients had acut myocardial infarc tions, and one had arteriosclerotic heart disease with pulmonary emboli but the fourth patient was a 39-year-old man with gram-negative septicemia and no pre-exist ng heart disease

infarction do not always show impairment of cardiac function do patients with shock of other etiologies always exhibit normal function It has been amply demonstrated in experimental hemorrhagic shock that cardiac deterioration may be an impor tant pre terminal event [13] Clinically severe myocardial impairment may be demon strated in young previously healthy pa tients during gram negative septicemia (Fig 1) Although heart failure may frequently be a late manifestation of "irreversible shock of any cause it sometimes occurs at a stage when prompt treatment can be effective Therefore the clinical syndrome of shock, whether precipitated by a myocardial infarction or another medi cal disease may be associated with normal or severely impaired cardiac function.

The salutary effect of volume expansion in some patients with myocardial infarction shock should not be too surprising Measured blood volume is often reduced [4] particularly in patients with evidence of severe vasoconstriction [24] The sudden fall in cardiac output and arterial pressure which probably accompanies an acute myocardial infarction may evoke reflex adrenergic discharge and vasoconstriction which may restore a normal or even elevated arterial pressure The resulting venoconstriction narrows the capacitance vessels and in creases capillary hydrostatic pressure [12] which leads to transudation of plasma out of the vascular space and perhaps also to trapping of red cells and plasma in areas of sluggish flow Although cardiac filling may be temporarily augmented by the venoconstriction the end result of prolonged vasoconstriction is a reduction in circulating volume and a low cardiac out put Even if myocardial function now returns toward normal as it may often do within a short time after infarction [7] cardiac output cannot increase until venous return is augmented

The level of the peripheral resistance in shock depends in large part on the criteria used in the selection of patients. If one accepts only individuals with cool moist skin and rapid thready pulses calculated total systemic vascular resistance will usually be high If patients with hypotension warm skin and slow pulses are in cluded resistance will often be normal or low Since a fall in cardiac output and ar terial pressure should be sensed by arterial baroreceptors and induce reflex vasoconstriction and cardiac stimulation why do some hypotensive patients exhibit slow heart rates and normal or low total periph eral resistance? The observations of low resistance in myocardial infarction shock have led to the search for vasodilator substances or cardiac reflexes which may in hibit adrenergic reflex effects. However a low cardiac output and hypotension with out an elevated total peripheral resistance or tachycardia is not unique to patients with myocardial infarction A similar hemodynamic pattern was observed by Rushmer in conscious dogs exposed to hemorrhage[1] and also occurs in hum n beings with other medical illnesses. Since these wide variations in the degree of reflex response to hypotension are observed in animals and man after di erse stresses, it is likely that indi idual differ

ences in patterns of cardiovascular response are at least partly responsible. Low resistance hypotension appears to be most common in patients with severe underlying diseases such as malignancy diabetes, and cirrhosis which may *impair adrenergic* reflex activity It is also possible that the degree of adrenergic vasoconstriction which develops in a given individual may depend on such things as heredity age, stiffness of the vascular walls and social and emotional factors. Thus, one might expect the wide spectrum of responses observed in myocardial infarction shock from the typical shock syndrome of intense cutaneous vasoconstriction to the clinical picture of hypotension and warm skin which many physicians do not call shock. These patients all have low cardiac outputs which may affect organ perfusion and lead to progressive circulatory deterioration. The only difference may be in the way their vascular systems have reacted to this stress.

If all patients with hypotension or inadequate blood flow after a myocardial infarction are said to have cardiogenic shock" the tendency might be to assume similarity from patient to patient and to apply the same therapy to all It is now clear that this approach to management is not consistent with the facts. Some patients who have intense vasoconstriction and normal cardiac function at the time they are seen will respond dramatically to plasma volume expansion In others without much reflex vasoconstriction infusion of a sympathomimetic vasoconstrictor agent may afford temporary circulatory support. In those with impaired myocardial contractility treatment may be instituted with digitalis, isoproterenol or even adrenergic blocking agents or mechanical cardiac assistance. The indications for each intervention should be clear and the responses of the patient closely monitored Only by this physiological approach is it likely that the high mortality rate in patients with myocardial infarction shock can be significantly lowered.

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Clinical communications

The normal atrial electrocardiogram: Morphologic and quantitative variability in bipolar extremity leads

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Despite the remarkable progress which has been made in clinical electrocardiography during the past half century, a number of neglected areas remain. One of these is atrial activation and repolarization. With a few notable exceptions, most clinical laboratories have not attempted to explore the details of electrocardiographic P waves. Even less attention has been devoted to the analysis of atrial recovery as manifested by the so-called T_P wave.

With the introduction of modern signal processing methods into biomedical research it has become possible to obtain and examine electrocardiographic deflections in fine-grained detail. A technique which holds great promise in the area of clinical application is the removal of random noise from repetitive signals by the averaging of successive waveforms. Relatively small devices designed for this purpose are commercially available and have already been applied with good effect to the ST-T complex of the exercise electrocardiogram, the P wave, and the fetal electrocardiogram.[1-4]

This report describes our own experiences in applying such a device to a detailed study of the P-T_P complex in a group of normal individuals. The material to be presented will deal with some new quantitative aspects of these deflections as well as with their morphologic characteristics.

Methods and materials

Forty-seven subjects free of known heart disease were selected for study. As indicated in Table I, the great majority of them were youthful adults. Bipolar extremity leads, I, II, and III, and the impedance respirogram† of each of the subjects were recorded simultaneously on magnetic tape for 20 minutes. In order to enhance the quality of the electrocardiographic waveforms, each lead was played back into a small special-purpose computer‡ which improves the signal-to-noise ratio of a recurrent signal by averaging out its random noise content. The averag-

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†Respirometer Model 211, Bio-Physical Instruments, Inc., Houston, Tex.
‡Model NS-513, Northern Scientific Instrument Co., Madison, Wis.

Table 1 Distribution of subjects by age and sex

Age (yr)	Male	Female	Total
15-24	21	5	26
25-34	14	0	14
35-44	3		5
45-54	0	0	0
55-64	1	1	2
Total	39	8	47

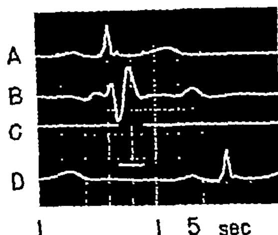


Fig 1 Method of establishing fiducial mark for processing the trace *D* electrocardiographic signal. Trace *A* is monitor signal reproduced from magnetic tape by an advance playback head The monitor signal is further amplified, time-differentiated, hea ily smoothed, and fed inverted int Schmitt trigger hich trips t the negative lev l indicated by the notching and lamping that appears on the downstroke of trace *B* The trigger in turn, acta tes time-delay ircuit hich is represented by the inverted square wa in trace *C* The offset of the square initiates a 400-millisecond period of signal eraging hich, t the setting which is hown, includes the latter one third of TP base line, the P T complex, and all of QRS.

ing procedure was performed twice for each lead once for those complexes occurring toward the height of normal inspiration and again for those occurring toward the depth of normal expiration A gating circuit which was adjusted to the respirometer signal permitted this discrimination of the respiratory phases.

Since the electrocardiographic signal is not exactly periodic some means was needed for accurately superimposing successive waveforms in the averaging process. Fig 1 illustrates some of the details of a time justification procedure which was suggested to us by Cox. On playback an anticipation head reproduces a monitor signal (trace *A*) approximately half a second in advance of the signal from which the noise is to be averaged out (trace *D*) The monitor signal is further amplified after which the effects of base line instability are minimized by a differentiating operational amplifier The inverted time derivative signal is hea ily smoothed by a low band-pass filter having a cutoff of 24 db per octave and is fed into a Schmitt trigger n the form shown in trace *B* At a given negative level shown by the notching and clamping which appears on the downstroke of trace *B* the trigger actuates an adjustable time-delay circuit as indicated by the inverted square wave in trace *C* The offset of this time-delay signal serves as a fiducial mark for the digital processing of each ind vidual beat of the trace *D* signal.

The effect of signal processing is illustrated in Fig 2 The top row of the figure shows single atrial complexes of Lead I II and III data as they are recovered from the magnetic tape on direct playback. Each of the centrally located deflections in these three panels is a P wave reproduced at ten times the conventional amplitude and time base scale factors. A certain amount of noise is evident in the traces and in some areas it is virtually impossible to distinguish between this noise and the morphologic details of the P wave

Successive beats are digitized by the special-purpose computer at the rate of 1,280 samples per second with an amplitude resolution of 00 steps of 5 microvolt each per centimeter Since the averaging procedure is based on comparison logic the amplitude of the final wa eform is ndependent of the number of beats so processed In addition a coarse-grained image of the waveform can be built up in computer memory from the first six or seven beats ("quick approximation" row of Fig 2) after which the grain adjustment of the device is set to intermediate and final smoothing positions. After final

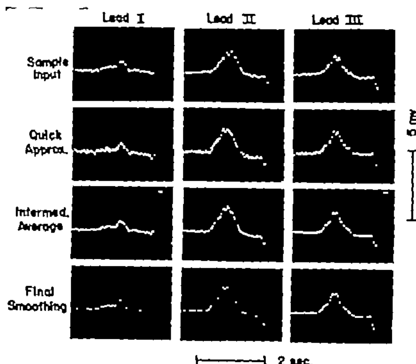


Fig. 2. The effect of signal processing by a small special-purpose computer. The central deflection in each panel is a P wave reproduced with tenfold expansion of the conventional amplitude and time-base scale factors. The upper row shows single complexes as they appear on direct playback from magnetic tape. The second row shows the rough waveform images which are built up in computer memory by playing back six or seven waves with the instrument in the "quick approximation" position. Continued playback at finer-grained control settings result in the intermediate average and "final smoothing" signal images. The procedure reduces random noise to approximately 1.0 root-mean-square microvolt referred to system input. Note also, the straightening of II base line segments.

smoothing, the contents of memory are photographed from the face of a cathode-ray oscilloscope as graphic records. The same information is dumped from memory onto punch cards for further computer processing. The digitized nature of the information is evident from the dotted structure of the QRS complexes in Fig. 2 and similar illustrations.

Results

There were 71 members in the original group of subjects. In all subjects the P wave forms were visually monitored during playback by careful observation of a cathode-ray display tube. Twenty-four members of the entire group showed distinct to suggestive changes in P wave amplitude which occurred with a periodicity of a few minutes. Their tapes are being held in reserve for further analysis by more advanced kinds of data processing. The remaining 47 tapes were smoothed during the inspiratory and expiratory phases in the manner described above.

The value of the averaging procedure in improving signal quality is well exemplified in Figs. 2 and 3. In Fig. 2 numerous coarse and fine deflections appear on the gently rising anacrotic limb of the unprocessed Lead II wave. The smoothing procedure clearly reveals in the lower left panel of the figure that some of these deflections are signal components rather than noise. An interesting contrast is to be seen in the Lead III series, in which there is stepwise reduction of several coarse notches from the downstroke of the P wave. The original recording is about as quiet as can be obtained with careful technique applied to a well relaxed subject. Noisier records benefit proportionately more from the averaging process.

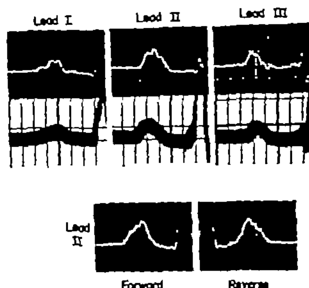


Fig 3 Comparison of processed P waves (upper row) with the same waves as recorded by a standard clinical electrocardiograph (second row) and optically magnified to about the same scale. The loss of detail which is evident in the standard tracings is discussed further in the text. The lower two panels illustrate that the same morphologic details are revealed by signal averaging whether playback be in the forward or reverse mode.

In Fig 3 the averaged Leads I II and III P waves of another subject are compared with those in conventionally recorded and optically magnified leads of the same subject. It is readily apparent that the fine details are not faithfully reproduced by the standard clinical instrument. Some loss of P wave amplitude in the conventional tracings is also evident, as is the virtual loss of the small Q waves at the beginning of each ventricular complex. The lower two panels in Fig 3 compare the averaging procedure with the tape played back in the forward and reverse directions, respectively. In both cases the fine structural details, such as the small slur plateau and notch which occur successively on the upstroke of P are equally well preserved.

The most striking qualitative feature of the enhanced P waves is the richness and variety of their notching. Some aspects of this characteristic have already been alluded to in the descriptions of Figs. and 3. Additional examples are shown in Fig 4. In all cases there is at least one clear-cut notch and in some cases there are as many as four as in Lead III of Subject 13. In the series as a whole there tended to be two notches per wave but a relatively large number of three notch examples was also noted. There seemed to be no regular pattern of distribution in some instances notching was limited to the upstroke, in others to the downstroke and in still others it involved the P wave anywhere from its middle portion to its entire extent. In only a few instances, as in Lead III of Subject 43 (Fig 4) was there a sizable notch in mid portion which seemed as though it might separate the P wave into right and left atrial phases.

Greatly enlarged digital printouts of the atrial deflections were prepared as a computer assisted means of determining P wave and P R-segment duration. Although there was no difficulty in visually recognizing the onset of QRS on these plots there was sufficient residual graininess in the data, as is illustrated in the left-hand panel of Fig 5 to obscure the exact onset of P. Therefore 25 data points of each lead in the region of P wave onset were subjected to a numerical procedure[7] which filters out without phase shift all signal components of 60 or more cycles per second. The effect of this low pass filtering is shown in the right-hand panel of Fig 5. By this means, we seem to be able to recognize the onset of P to within three

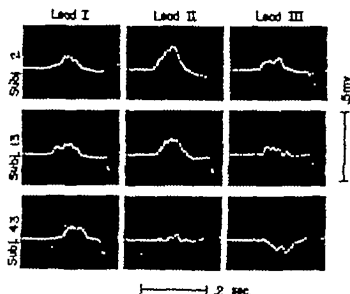


Fig. 4. Examples of the richness and variety of notching which signal processing reveals in normal P waves. Lead III of Subject 43 shows a large notch in mid-portion which seems to separate the deflection into right and left atrial phases. However, very few of the records showed this kind of separation, and no distinctive pattern of notching could be recognized in the group as a whole. The digitized nature of the signals is evident in the discontinuous structure of the QRS complexes.

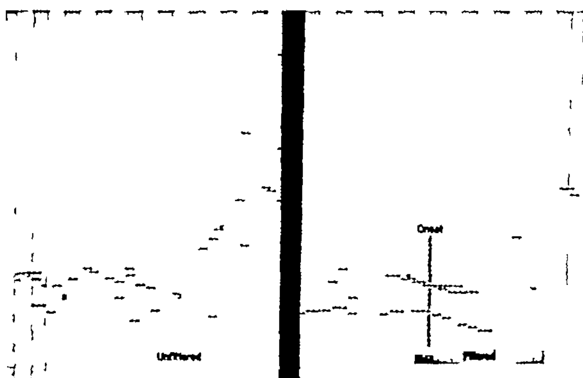


Fig. 5. Overplotted digital point output of Lead I, II, and III signals in the region of P wave onset. As illustrated in the left-hand panel of the figure, the average waveforms contain enough residual noise to interfere with accurate recognition of P wave onset. As is shown in the right-hand panel, this difficulty is reduced by numerical filtering, without phase shift in the region of onset.

sample points i.e. with an accuracy of ± 2.5 milliseconds.

Determining the temporal point which marks the ending of P and the beginning of the T_P deflection posed some problems, since there is no phase of manifest quiescence corresponding to the S-T segment of ventricular repolarization. Similarly base line crossing by the downstroke of the P wave did not seem to be suitable for marking this event because of phase differences between the three leads. Accordingly a simple computational device was developed in which the termination of the P wave is taken as that point in time at which the angle between successive instantaneous atrial vectors and the mean P vector as computed cumulatively from all preceding instantaneous vectors, changes from acute to obtuse. This kind of decision making avoids the difficulties referred to above but is necessarily somewhat arbitrary since atrial recovery is well under way before the excitation phase has been completed

The onset of P was taken as the earliest detectable deflection in each set of leads and the end of the P R segment as the datum sample immediately preceding the latest onset of QRS These points, together with the computer-decided P offsets gave a value of 99 4 ± 12.5 milliseconds for P wave duration and 61 6 ± 16.5 milliseconds for P R-segment duration. The respective intervals are approximately 25 per cent longer and shorter than those that are ordinarily employed in diagnostic electrocardiography These differences are almost certainly due to the increased resolution of the fine-grained technique used in this study

Mean P vectors in the frontal electrocardiographic plane computed from the punch card signal data, are illustrated as a scattergram in the lower right quadrant of Fig 6. A bivariate method of analysis was used in which the major and minor half axes of the two concentric ellipses represent 1 and 2 standard deviations along the principal axes of distribution Similar treatment was given to atrial recovery forces with the sequence of observation points necessarily limited by the onset of QRS. The scattergram of these mean "T " vectors is presented in

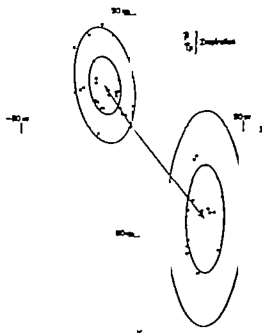


Fig 6 Scattergram of mean P (*solid dots*) and mean T (*open dots*) vector termini in the frontal electrocardiographic plane The figure was prepared from waveforms which were averaged toward the height of normal inspiration. The results are not statistically different from those obtained by signal processing limited to the expiratory phase The major and minor half-axes of the concentric ellipses represent 1 and 2 standard deviations along the principal axes of distribution. The figure shows that the biologic variability of these two vectorial parameters roughly parallels that of mean QRS and T vectors. Individually and as a group the mean P and T vectors have opposing orientations.

the upper left quadrant of Fig 6 and the group-average values with standard deviations are given in Table II The average P T_P angle was 184 ± 21 degrees.

The results of this analysis appear to be noteworthy in two major respects first for the relatively wide scatter of the mean vector termini and second, for the relative constancy of the P T angle The latter is the less surprising of the two findings, since it is commonly appreciated that P R segment deflections although usually of low amplitude tend to be directed oppositely from the P wave. On the other hand variations in the P axis seem to be

Table II. Atrial ECG metrics

Interval—millisecond			
P	99.4 ± 12.5	T	61.6 ± 16.5
Magnitude—microvolts			
$\bar{P}$	31.0 ± 7.9	$\hat{P}$	41.9 ± 22.2
$\bar{T}$	−11.9 ± 6.7	$\hat{T}$	−18.7 ± 12.7
P-T angle	184.2 ± 21.3 degrees		

less well appreciated in clinical electrocardiography, and yet Fig. 6 bespeaks a diversity of mean P and T_P orientation which approaches that of mean QRS and T vector forces. Looking at these relationships somewhat retrospectively, one might expect to find the same order of biologic variability in dealing with excitation and recovery in the atria as compared to the electrocardiographic manifestations of these same processes in the ventricles.

Discussion

Although the technical quality of the conventional electrocardiogram is greatly impaired by the inherent limitations of the instrument which produces it, careful correlative studies of the P wave with clinical and pathologic information continue to yield valuable diagnostic information.[1-12] Records of better quality may be obtained by the use of equipment having greater sensitivity and an extended range of frequency response.[13] The use of digital computer techniques, including the application of appropriate signal processing methods, further improves the signal by reducing its random noise content and greatly facilitates quantitative treatment of the waveform data.

The smoothing procedure has already been found to be valuable in improving the legibility of the ST-T portion of the exercise electrocardiogram.[3] Our own experiences with the technique nicely confirm Irisawa and Seyama's observations of its effectiveness when applied to the atrial electrocardiogram. Furthermore, we have noted a fairly satisfactory minimization of base-line wandering. The effect is evident in several of the illustrations, in which it may be noted that the portion of the base line which precedes the P onset tends to be quite straight and virtually horizontal. As a test of residual noise, we fitted parabolic curves to 0.08-second segments of the rectified base lines by the least-squares method. The second-degree coefficients of the fitted curves were quite small, giving ample support to the visual impression of rectilinearity. Residual noise determined by this means amounted to approximately 1.0 root-mean square microvolt, referred to system input.

The finding that the mean P and T_P vectors of a given subject are likely to be oppositely directed is well in accord with the generally held belief that the order of atrial repolarization follows that of depolarization. No effort was made to determine atrial gradient, since the observations during repolarization are necessarily terminated at the onset of QRS. We have not been able to devise a satisfactory method of dealing with this vexing obscuration of desired information. In an interesting attempt, however, the lead axis of each subject was numerically rotated to the position of maximum-amplitude T_P display. The resulting P-R segments were fitted with second-degree curves, which were extrapolated in the direction of increasing time until they reached base line.

Six representative examples of the extrapolation procedure are shown in Fig. 7. The extrapolated portion of the upwardly concave curves did not extend beyond the QRS complex in any subject, which suggests that the level of the S-T-segment junction is not influenced by atrial repolarization in normal subjects. In 3 cases the fitted curve could not be extrapolated because of downward concavity. In all 3 instances, however, P-R amplitude was so small (panel 6 of Fig. 7 shows the largest of them) that encroachment of T_P forces on the S-T segment seems to have been unlikely. Since the ratio of extrapolated to visible T_P area is rather variable, the original intent of determining a correction factor for mean repolarization vector amplitude was abandoned.

Tape playback in the reverse direction simplifies the averaging technique by removing the need for an advance head and a time-delay circuit. The quality of pattern is equally good, and the accu-

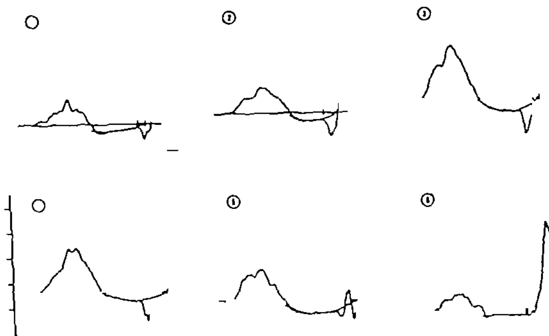


Fig 7 Several examples of trial complexes in which numerical rotation has been used to maximize the area between base line and P R segment In the first five panels the obscured terminal portion of atrial repolarization has been roughly pproximated by the least-squares fit of a parabolic curve to the P R segment, with extra polation of the curve t base line. Although the extrapolated segment crosses the base line t variable locations, it does not encroach upon the S-T segment 1 3 cases, of which the sixth panel is a example, the fitted curve could not be extrapolated because of downward concavity Because of low-amplitude P R deflection in these 3 cases it is believed to be nlikely that atrial repolarization extended beyond the QRS complex. The scale marks are equivalent to the millimeter blocks of conventional electrocardiograms recorded t standard scale factors of 1 0 millivolt and 0.4 second per centimeter

tomed left to-right inscription can be readily restored by reversing connections to the horizontal deflection plates of the cathode-ray oscilloscope An apparently minor objection is that part of the QRS and all of the S-T is lost in reverse play back, since the action of the averaging device triggers on "SRQ

The quantitative parameters reported in this paper were derived from atrial waveforms processed during inspiration. Small statistically insignificant differences were noted between these and the same parameters determined for the expiratory phase. Thus, the technique of gating on the respirometer signal does not seem to materially improve this kind of data quantification. On the other hand as is illustrated in Fig 8 ind vidual waveforms are likely to show small but distinct dif ferences between the two phases of respiration Therefore we have decided to retain the technical feature of gating on respiration, pending a more detailed investigation of the beat by-beat reproducibility of the P T_P waveform

Summary

Leads I II and III atrial electrocardiograms of 47 normal subjects were prepared by modern signal processing methods at a tenfold expansion of the conventional amplitude and time base fac tors. After processing the waveforms were reproduced in both graphic and digital punchout forms. The procedure provided a reliable reference level by stabilizing the base line and reduced over all random noise content to approximately 1 0 root mean-square microvolt, referred to system input.

Qualitative appraisal of the records showed the P waves to be richly notched and slurred The number of distinct notches per wave varied from one to four Notching suggestive of separation into right and

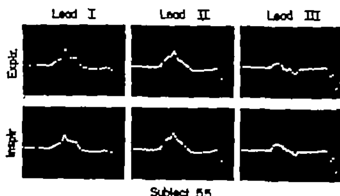


Fig 8 Influence of the respiratory cycle on atrial waveforms The three leads in the upper row were averaged during expiration those in the lower row during inspiration Lead I shows comparatively greater peak amplitude of P during expiration, together with a more pronounced plateau on the downstroke In Lead III notching in the mid portion of P is deeper during expiration, and the terminal deflection of the wave is more negative. These are relatively minor differences which do not significantly affect the temporal and mean quantitative parameters of P and T

left atrial depolarization phases was present in relatively few subjects.

Quantitative studies included determination of P wave and P R segment duration the magnitude and orientation of mean P and T_P vectors in the frontal electrocardiographic plane, and P T_P angles. Scattergrams of the mean vector termini reveal a distribution which roughly parallels that of mean QRS and T vectors in extent. Similarly the angle between the two vectors is the most nearly invariant parameter of this kind In contrast to ventricular behavior however the atrial activation and recovery vectors are oppositely directed

The terminal portion of the atrial recovery phase is obscured to a variable extent by ventricular activity Extrapolation of the P R segment was attempted by arbitrarily fitting second-degree curves to the recognizable portion of T_P The results suggest that atrial recovery forces do not encroach upon the S-T segment in normal individuals.

We are greatly indebted to Harry A Phillips and Charles O Eddlemon for invaluable technical assistance

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Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques

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Coxsackie viruses have been isolated from patients with a variety of illnesses, particularly those associated with acute myocarditis, aseptic meningitis, epidemic myalgia, pleurodynia, and herpangina. Studies reported recently from this laboratory showed a high incidence of viral valvulitis and myocarditis in mice and monkeys infected with Coxsackie virus B4.[1-3] The immunofluorescent technique used in these studies showed that specific viral antigen can be demonstrated in valves, mural endocardium, myocardium, and epicardium with fluorescein-labeled hyperimmune rabbit serum. The presence of antigen was associated with an inflammatory valvulitis and myocarditis in all instances.

Human viral endocarditis and valvulitis as well as myocarditis, both acute and chronic, may be more common than indicated by the current literature. It seems very likely that many instances of viral carditis are overlooked. The short duration of Coxsackie virus disease and its clinical manifestations resemble so many other respiratory infections that the nature of the disease usually goes unrecognized. Further more, virus isolation has not as yet been adapted for use as a routine clinical procedure. In addition, Coxsackie viral infections frequently may be subclinical in both the acute and chronic phases. Despite these difficulties, however, a number of viruses have been recovered from man by in vitro cultivation of cells from various organs collected in association with a variety of diseases.[4]

We have suggested that certain chronic valvular diseases and cardiomyopathies presently considered to be of unknown cause may be produced by a variety of cardiotropic viruses.[7] The present study was undertaken in an attempt to explore, by means of immunofluorescent techniques, the possibility that the Coxsackie B viruses may be the cause of some forms of chronic valvular, myocardial, and pericardial dis-

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ease in man Autopsy material of heart tissue gathered at routine necropsies from the Charity Hospital at New Orleans, and derived mainly from young patients was examined The results of these investigations are presented as well as a discussion of the significance of the findings.

Material and methods

The material in this series consisted of heart tissues from 55 routine autopsies performed between January and June of 1966 at the Charity Hospital of New Orleans. Hearts were randomly selected from 40 young patients varying in age from still birth to 30 years. Cardiac tissue was also collected from 15 patients of middle age with fibrotic lesions of the mitral valves. Thirty patients were male and 25 female. Forty patients were Negro and 15 white

Samples of heart tissue were selected from the upper lateral aspect of the left ventricular wall The sections included a part of the mitral valve The hearts had been refrigerated at the morgue for 6 to 24 hours. Each specimen collected for immunofluorescent antibody staining was trimmed to an appropriate size and frozen in isopentane and dry ice for cryostat sectioning The remaining portion was fixed in 10 per cent formalin for routine histologic sectioning and hematoxylin-eosin staining

Five different types of hyperimmune rabbit antisera to Coxsackie viruses B B B_3, B_4, and B were prepared by two injections of different adult rabbits with live viral antigen suspensions grown in a medium composed of cells of monkey s kidney The inhibition titers of the different lots of pooled sera varied from 1 64 to 1 723 The sera were fractionated with one third saturated ammonium sulfate and the globulin conjugated with fluorescein isothiocyanate After passing through a G-50 Sephadex column in 0.01M phosphate buffer at pH 7.4 the conjugated antisera were absorbed twice by a powder of dry rat liver in preparation for direct immunofluorescent staining

Aliquots of nonconjugated antisera from the same preparations were saved for use in the indirect method of study with fluorescein labeled antirabbit globulin prepared in sheep. Control antiserum to proteins of monkey kidney was prepared in other rabbits by two intravenous injections of suspensions of virus-free monkey kidney The serum was treated in the same manner and used for control staining in both the direct and indirect methods.

The direct method of staining was used throughout for screening the heart tissue for the presence of viral antigen Six sections from each case were stained with the conjugated antisera to the five different types of Coxsackie B group as well as with the antiserum from the control rabbits

The indirect method of staining was applied to the sections of the positive and suggestively positive cases noted by direct fluorescent antibody staining for further confirmation This check was carried out because the indirect method offers certain advantages due to generally less prominent nonspecific reactions with increasing dilutions of the sera The technique outlined by Cherry and associates was used

A Reichert microscope and illumination system were used with appropriate ultraviolet light source and filters.

Specificity of staining was carefully evaluated The frequent presence of nonspecific tissue fluorescence observed in the usual fluorescent antibody preparations imposed some difficulties in the interpretation of the positive finding However since the virus particles of the Coxsackie B group have a specific intracytoplasmic localization the cytoplasmic site of the fluorescence was the *most important and ultimate criterion used for the interpretation and confirmation of a* positive finding Usually it was readily apparent from the morphologic appearance whether myofibers or fibrocytes contained the cytoplasmic antigen The scattered weak cytoplasmic fluorescence of small round cells in the myocardial interstices was considered to be a nonspecific reaction of inflammatory leukocytes. The specificity of staining was unique in both the direct and indirect methods and no similar cytoplasmic fluorescence was noted when the control serum was used in either the direct or indirect method.

Results

A total of 17 hearts from the 55 autopsies of different age groups were positive for Coxsackie B viral antigen within the myocardium Three of the 17 hearts showed an

*Table I. Age incidence of Coxsackie viral myocarditis and mitral valvulitis determined by the immunofluorescent antibody method**

Age	No. of patients studied	Patients with positive myocarditis		No. of patients with associated valvulitis
		No.	Per cent	
Less than 1 mo.	14	5	35 71	1
Less than 1 yr	12	3	25 00	0
1–15 yr	8	6	75 00	1
16–30 yr	6	1	16 66	0
31–45	7	0	0	0
46 over	8	2	25 00	1
Total	55	17	30 90	3

*Findings in 17 patients in screening study of 55 hearts from consecutive autopsies.

associated mitral valvulitis. The results are summarized in Table I. The diagnosis depended upon the demonstration of viral antigen within either the connective tissue cells of the valves or isolated myofibers. Focal interstitial myocarditis was demonstrated by hematoxylin-eosin staining in sections from all patients in whom immunofluorescent viral antigen was detected within the myocardium (Figs. 1 to 4).

Of the 8 randomly selected hearts from the patients in the 1- to 15-year age group, 6 showed chronic myocarditis and 1 had an associated chronic mitral valvulitis with immunofluorescence specific for Coxsackie antigen. In the group of neonatal deaths (ages less than 1 month) specific viral antigen was found in the myocardium of 4 patients and the antigen was present in both the myocardium and mitral valve of 1 patient. The incidence of positive findings was much less in the adult groups. Most of the patients in this group, however, were purposely selected on the basis of gross thickening of the mitral valve cusps.

Of the 17 positive cases, 15 were Negro and 2 were white. Sex distribution was essentially equal: 8 were male and 9 female.

The 17 positive cases were divided into 4 groups according to the patients' clinical features (Table II). Two were classified as premature, had congenital anomalies, and 11 had infectious diseases (etiology undetermined) with a variety of clinical manifestations and a short period of hospitalization before death. The remaining 2 cases were assigned to a miscellaneous group: 1 patient had died of an extensive third degree burn and the other of long-standing hypertensive cardiovascular disease with cardiomegaly and nonspecific mitral valve thickening. Except for 1 patient in the infectious disease group clinically diagnosed as having "viral encephalitis," none of the groups studied had reliable clinical or laboratory evidence of viral infection. The cause of death in a significant number was frequently complicated by respiratory infections.

One of the 17 patients, a male Negro, had clinical and pathologic evidence of idiopathic cardiomegaly with nonspecific fibrotic thickening of the mitral valve. Coxsackie B_4 viral antigen was identified in both the mitral valve and myocardium. In another patient with cardiomegaly considered clinically to be hypertensive in nature, Coxsackie viral B_1 and B_2 antigens were found within the myocardium. The 2 patients with congenital anomalies (one with a large patent ductus arteriosus and the other with microcephalus and minor anomalies of the vascular branches of the aortic trunk) were found to have Coxsackie viral antigen within the myocardium. The hearts from the remaining 13 patients which were positive for viral antigen showed no especially significant gross pathologic changes.

The microscopic features of the immuno-

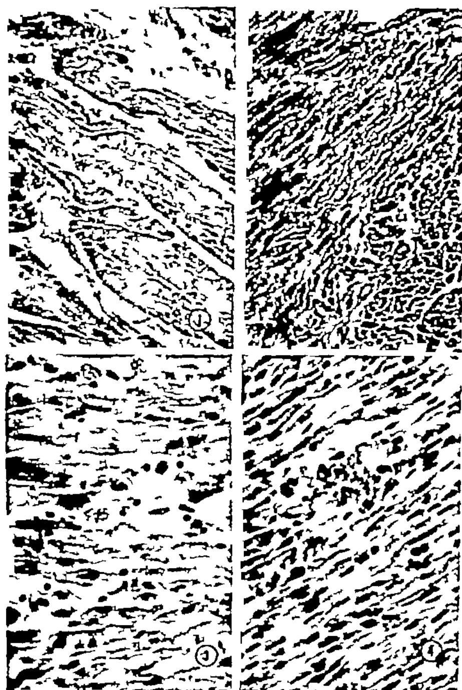


Fig. *1* Section of myocardium from Patient 135 36-year-old Negro man with interstitial myocarditis, show round cell infiltration, edema and fibrosis in the interstices. (Hematoxylin and eosin × 120.)
Fig. 2 Section of myocardium from Patient 63 1 year-old Negro boy with interstitial myocarditis show interstitial cell infiltration and edema with necrosis of muscle fibers. (Hematoxylin and eosin. × 120.)
Fig. 3. Section of myocardium from Patient 79 11 year-old Negro girl with chronic myocarditis and isolated necrosis of muscle fibers. (Hematoxylin and eosin × 480.)
Fig. *4* Section of myocardium from Patient 40 premature stillborn Negro boy with focal myocardial necrosis and mild interstitial round cell infiltration. (Hematoxylin and eosin. × 480.)

Table II. Clinical and pathologic correlations for the 17 patients showing immunofluorescence specific for Coxsackie B viral myocarditis and valvulitis

Patient No.	Age	Sex and race	Clinical manifestations	Time in hospital (days)	Pathologic finding	Immunofluorescence finding
Group I. Prematurity (2 out of 9 patients)						
40	0	M N	Premature stillbirth	0	Prematurity	Coxs. B_4, B myocarditis
45	23 days	M N	Prematurity	23	Pneumonia	Coxs. B myocarditis
Group II. Congenital anomalies (2 out of 6 patients)						
57	7 mo.	M N	Congestive heart failure	9	Congenital microcephalus	Coxs. B B myocarditis
53	2 days	M N	Cyanosis		Widely patent duct arteriosus	Coxs. B B myocarditis
Group III. Infections (11 out of 25 patients)						
140	3 days	M N		3	Bronchopneumonia	Coxs. B_4, B B myocarditis Coxs. B valvulitis
153	7 wk.	F N	Diarrhea	—	Pulmonary edema	Coxs. B_4, B myocarditis
87	7 days	F N	Watery diarrhea	2	Gangrenous enteritis	Coxs. B_4, B myocarditis
20	4 mo.	F N	Fever, vomiting, lethargy	3	Tracheobronchitis, pulmonary edema	Coxs. B B B myocarditis
63	1 yr	M N	Malnutrition and dehydration	2	Pneumonia	Coxs. B_4 myocarditis
152	1½ yr	F N	Fever, stiffness of neck, respiratory distress	1	Interstitial pneumonia, suggestive myocarditis, lymphadenopathy, hepatomegaly	Coxs. B myocarditis
151	1 yr	F N	Irritable, vomiting, disorientation	2	Cerebral edema, pleural adhesion, patchy atelectasis of lungs, petechial hemorrhage of thymus gland	Coxs. B myocarditis
155	5 yr	F N	Diarrhea, malnutrition	—	Cerebral edema, bronchopneumonia	Coxs. B B myocarditis Coxs. B valvulitis
96	6 yr	F N	Irritable, vomiting, high fever	1	Edema and congestion of brain, hemorrhagic pneumonia, septic splenitis, and petechial hemorrhage of myocardium	Coxs. B_4, B myocarditis
135	26 yr	M N	"Viral encephalitis"	16	Brain edema, bronchopneumonia	Coxs. B B myocarditis
129	55 yr	M N	Epistaxis, fever, cardiomegaly, pancreatitis, azotemia	35	Idiopathic cardiomegaly, hydrothorax, pancreatitis	Coxs. B myocarditis Coxs. B valvulitis
Group IV. Miscellaneous group (2 out of 15 patients)						
5	53 yr	F W	Hypertension, hemiplegia	70	Cardiac hypertrophy, mural thrombosis, fibrous thickening of mitral valve	Coxs. B B myocarditis
79	11 yr	F N	Third-degree burn	6	Lobar pneumonia, third degree burn of skin	Coxs. B_4, B myocarditis

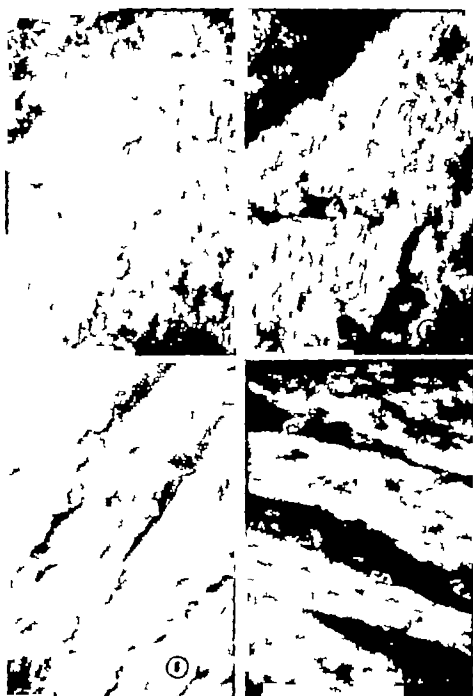


Fig. 5. Section of myocardium from the same patient [illegible] Fig. 4 shows (*A*) bright cytoplasmic immunofluorescence spec[illegible] for [illegible] tigen of Coxsackie [illegible] irus B in muscle fibers by means of the indirect fluorescent [illegible] tibody technique (IFA) (× 480) and (*B*) lack of fluorescence in the control. Consult text for details.
Fig. 6. Section of myocard[illegible]m from Patient 8 [illegible] 7 [illegible] old Negro girl [illegible] hows (*A*) cyt[illegible]plasmic fluorescence [illegible] means of the direct imm[illegible]nofluorescent [illegible] tech[illegible]ique (DFA) (× 480), and (*B*) the prep[illegible] of serial sect[illegible]n from the same he[illegible]rt tissue bl[illegible]k. Not[illegible] the [illegible] nonspecific cytoplasmic [illegible] [illegible] stred, infiltrating leukocytes. (× 480.)

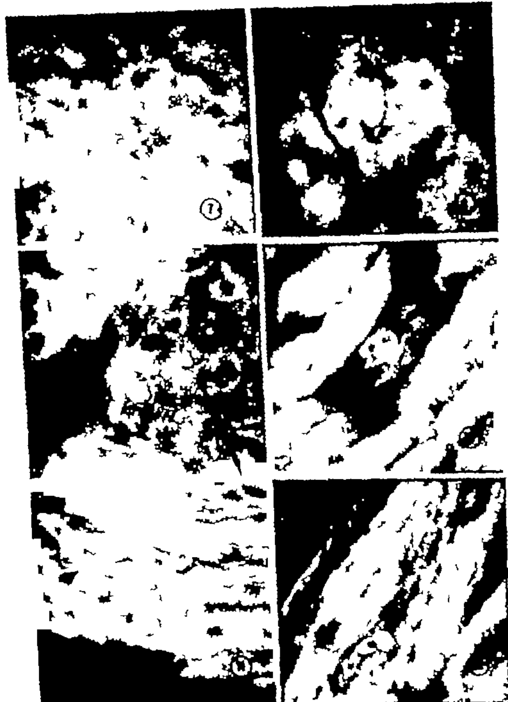


Fig. 7 Section of myocardium from Patient 140, a 3-day-old Negro boy, shows cytoplasmic fluorescence due to the presence of Coxsackie B antigen. The elliptical configuration may represent the eclipse phase of virus-cell interaction by means of the indirect fluorescent antibody technique. (× 480.)

Fig. 8 Section of myocardium from Patient 20, 4-month-old Negro girl, shows fluorescence specific of Coxsackie virus B filling the cytoplasm of an affected muscle fiber by means of indirect fluorescent antibody technique. (× 480.)

Fig. 9 Section of myocardium from Patient 140, a 3-day-old Negro male, shows cytoplasmic granular fluorescence specific for Coxsackie virus B_3 antigen in affected muscle fibers by means of indirect fluorescent antibody technique. (× 780.)

Fig. 10 Section of myocardium from Patient 5, a 33-year-old white woman, shows cytoplasmic fluorescence specific for Coxsackie virus B_4 antigen in segment of degenerating muscle fiber by means of the indirect fluorescent antibody technique. (× 780.)

Fig. 11 Myocardial section from Patient 140 shows cytoplasmic fluorescence specific for Coxsackie virus B antigen in an isolated, atrophic muscle fiber by means of the indirect fluorescent antibody technique. (× 480.)

Fig. 12 Section of myocardium from Patient 20 shows cytoplasmic fluorescence specific for Coxsackie B antigen in two deformed muscle fibers by means of the indirect fluorescent antibody technique. (× 480.)



Fig. 13 Section of mitral valve from patient 140 showing cytoplasmic fluorescence specific for Coxsackie virus B4 in fibroblastic connective tissue cells by means of the indirect fluorescent antibody technique (× 480.)
Fig. 14 Section of mitral valve from patient 129 showing cluster of cells containing fluorescence specific for Coxsackie virus B4 antigen in the cytoplasm by means of the indirect fluorescent antibody technique (× 480.)
Fig. 15 Section of the mitral valve from patient 140 showing inflammatory reaction featuring cellular infiltration and proliferation. (Hematoxylin and eosin × 480.)
Fig. 16 Section of the mitral valve from patient 129 showing inflammatory reaction (Hematoxylin and eosin × 480.)

fluorescent-positive hearts seem to have both quantitative and qualitative differences. The hearts of 2 patients from the group of neonatal deaths (one stillbirth and another a premature infant who lived for 7 days with sustained watery diarrhea) were found to be heavily infected that is to manifest strongly positive immunofluorescence (Figs. 5 and 6). Diffuse spotty cytoplasmic fluorescence was found throughout the myocardium of these patients. In the remainder of the hearts antigen-positive myofibers were patchy in distribution and fluorescence was usually noted to be located at one side of the unstained nucleus or filling the cytoplasm with only the nucleus "unstained" (Figs. 7 and 8). In some instances the cytoplasmic fluorescence displayed a finely granular pattern (Fig. 9). Frequently the fluorescent positive myofibers were markedly deformed (Figs. 10 to 12).

Of the three mitral valves showing immunofluorescence one showed a cluster of fluorescent positive cells within the connective tissue stroma (Fig. 13). The other two mitral valves revealed scattered cytoplasmic fluorescence with in fibrocytic cells (Fig. 14). Histologic study of the valves showed a chronic inflammatory reaction featuring mononuclear cellular infiltration and fibroblastic proliferation (Figs. 15 and 16).

The majority of the positive cases had more than one Coxsackie B group viral antigen in the myocardium. The most frequent combination was Coxsackie virus B_4 and B (5 cases).

Discussion

During the past decade an increasing number of patients with Coxsackie viral myocarditis have been reported. Usually only focal scattered interstitial myocarditis is noted in the postmortem material. These lesions are considered to be viral in nature. However since such lesions are usually small localized and widely separated they may often be overlooked. For instance Ma cure[9] had to section 10 blocks before definite lesions were found in 2 patients. In the routine histopathologic study of hearts only a few sections of the myocardium are examined. This constitutes an infinitesimally small portion of the whole myocardium. Thus the exact incidence of viral interstitial myocarditis is probably much higher than suggested by the present literature.

It is worth noting that the identification of occult viral agents by means of in vitro cultivation of cells from various organs and in association with a variety of clinical diseases, has been reported by several investigators. Gold and his associates[4] isolated a number of viral agents from 12 of 48 infants who had died suddenly and unexpectedly. Of these 12 patients, Coxsackie viruses were identified in 10. Benyesh-Melnick and associates[4] reported recovering a number of latent viruses from kidneys at autopsy when a systematic search was made in children who had died of a variety of illnesses. Valdes-Dapena and Hummeler isolated Coxsackie B virus from the lung of 1 infant who had no histological evidence of pneumonia.

It does not seem surprising to find a high percentage of Coxsackie viral myocarditis (30.90 per cent) and endocarditis (5.45 per cent) in routine postmortem material when a specific and sensitive method such as the fluorescent antibody technique is used. The "isolated" myocardial damage in individual myofibers which showed fluorescent antigen in the cytoplasm is particularly interesting. Scattered patchy interstitial cellular infiltration was frequently the only evidence which suggested viral infection was present when routine hematoxylin-eosin stains were used. Indeed previous reports indicate that a virus often can be isolated from tissues in which there is no histologic evidence of inflammation or infection.[1] Immunofluorescent techniques however readily reveal the presence of viral antigens within the affected cells. It seems much easier to identify a viral antigen by immunofluorescence than to recover living viruses by means of in vitro cultivation of infected tissue.

Since Coxsackie group B viruses are now increasingly recognized as a relatively frequent cause of myocarditis, it is apparent that Coxsackie B virus myocarditis is likely to be much more widespread than suggested in the literature. Since Coxsackie B viral myocarditis in infants is not always fatal subclinical or mild symptomatic manifestations of the disease may exist quite frequently in infants and children. The

clinical and pathologic data for the 17 cases of our stud (Table II) showed that the Coxsackie B viruses in the myocardium and or the mitral valves were not directly responsible for the death of all of the patients. However some of the neonatal deaths in our series may well have been the direct result of Coxsackie viral infection. Two case histories indicate that the Coxsackie virus infection may well have been acquired by the infants in utero or shortly after birth. Since a large majority (15 cases) of the hearts with positive Coxsackie B infection were from Negroes socioeconomic conditions may be a significant factor responsible for the high incidence of infection found in this stud

This study provides supportive evidence of the role of Coxsackie B virus infection in the etiology and pathogenesis of certain types of chronic valvular endocarditis in man. It has been suggested previously that chronic endocarditis or valvulitis could be a complication of viral infection. Three instances of chronic Coxsackie viral valvulitis were identified in this series with positive Coxsackie viruses B B and B antigen being found respectively in the mitral valves. In one instance a 55-year-old Negro man with clinical manifestations of ... fever cardiomegaly and pancreatitis as well as fibrotic thickening of the mitral valve on gross pathologic examination was found to have Coxsackie virus B antigen with inflammatory reaction in both the mitral valve and the myocardium. This may well represent a typical case of Coxsackie B viral chronic myocarditis associated with chronic viral valvulitis. In the other 2 patients with valvular lesions 1 a 3-day-old Negro boy and the other a 5-year-old Negro girl cardiomegaly was not found on gross pathologic examination.

It is still controversial whether viruses other than those of German measles are responsible for congenital anomalies. Two patients with cardiovascular congenital anomalies in our series were found to have Coxsackie B virus antigen within the myocardium. Although the findings are inconclusive in such a limited number of cases the possibility that Coxsackie B virus may cause some forms of congenital cardiac anomalies is highly intriguing. Since it is well known that this virus is highly cardiotropic for man especially infants, it is tempting to speculate that some stillbirths or premature deliveries could be induced by a transplacental infection with a Coxsackie B virus in the fetus. Even though only 2 out of our 9 cases of prematurity demonstrated the antigen 1 of them had the most severe myocarditis noted among the 17 positive cases. The incidence of Coxsackie virus infection in the prenatal and neonatal periods certainly needs further study

Gore and Saphir[22] in a study of 1,402 patients with myocarditis, were unable to establish an etiologic diagnosis in 75 per cent of them. Our findings strongly suggest that the Coxsackie B group of viruses may have accounted for a significant number of these

The question of the clinical significance of viral antigen within the myocardium and valves has arisen previously. It seems likely that viruses in these cells may exist dormant for long periods of time and become activated when the body resistance of the host is suddenly reduced by any number of factors including bacterial infections. This possibility is well supported by the behavior of the herpes simplex virus. In addition it seems that these hidden viruses may produce a mild chronic inflammatory reaction without any clinical symptoms and signs of heart disease. These latent viral infections may under certain circumstances, develop into an acute fulminating infection with rapidly progressive myocardial disease and death

These findings suggest that viral infection may be the cause of some forms of acute and chronic myocardial and endocardial diseases in man. Although most of the acquired chronic valvular disease is thought to be due to rheumatic fever we believe a viral etiology should be ruled out before a final diagnosis of post rheumatic valvulitis is considered established. This effort seems especially important in those instances, in which chronic valvular disease is present and in which no clinical history of previous rheumatic fever can be established. Further investigations are certainly indicated to clarify these relationships.

Summary

From a survey of 55 routinely autopsied hearts studied by means of the immuno-

fluorescent antibody techniques, Coxsackie B group virus antigens were found in the myocardium in 17 cases (30.90 per cent) and in both the myocardium and mitral valve in 3 cases (5.45 per cent). A chronic focal interstitial myocarditis was noted in all 17 cases upon routine histologic study. A high percentage of positive viral antigen was found in hearts of children (75 per cent) and infants (35.71 per cent). The criteria for positive immunofluorescent identification of antigen consisted of intracytoplasmic localization of the fluorescence in the affected myofibers and in fibrocytes of the mitral valves. Chronic Coxsackie virus valvulitis is shown to be present in man in certain types of unexplained chronic valvular heart disease. It is postulated that some instances of chronic valvular disease previously thought to be post rheumatic in origin may represent chronic viral valvulitis. These studies also suggest a possible role of the Coxsackie virus as a cause of some congenital cardiac defects and stillbirths.

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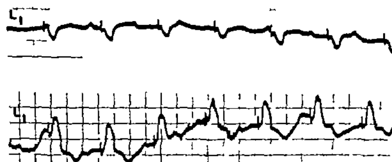


Fig. 2. Upper strip shows right bundle branch block with first right ventricular endocardial pacemaker. Lower strip shows left bundle branch block produced by pacemaker wires implanted in right ventricular myocardium.

Fig. 3. *Upper block.* Twelve-lead ECG shows right bundle branch block pattern produced by the first right ventricular endocardial pacemaker. *Lower block.* Standard leads show expected pattern of *left bundle branch* block produced by the second right ventricular endocardial pacemaker.

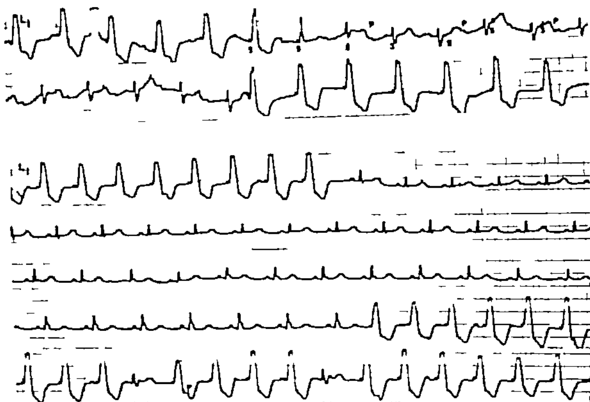


Fig. 4 The upper strips are continuous and contiguous, showing competition between sinus and artificial pacemaker. Note prolonged P-R interval of 0.36 second and deep slurred S wave in the sinus beats. The lower strips are continuous but not contiguous recordings made at a later time during the 1½-minute turnoff of pacemaker. Note normal P-R interval and absence of slurred S wave. In the last strip, after the pacemaker is again turned on, two sinus capture beats occur (first and fifth P), this time with a P-R interval of 0.64 second and again the slurred S wave. L_1, Standard Lead I. *P*, P wave. *S*, Pacemaker stimulus. *F*, Fusion beat.

beats are conducted with first-degree block and incomplete right bundle branch block. The transvenous pacemaker was turned off for 1½ minutes, yielding the tracings shown in the lower section of Fig. 4. The sinus node is seen to immediately control the heartbeat with normal P-R intervals and QRS complexes. Later, when the pacemaker is turned on again, two sinus captures are seen showing first-degree block (with skipped conduction) and incomplete right bundle branch block.

Discussion

Experimental stimulation of the ventricles has been observed to produce specific patterns. These have been patterns similar to right bundle branch block when the left ventricle was stimulated and left bundle branch block when the right ventricle was stimulated. These patterns were interpreted to mean that the impulse spreads directly through myocardial fibers and does not enter the conducting system.

The initial patterns in our first 3 cases indicate that the left ventricle depolarized early despite the delivery of the pacemaker stimulus to the right ventricular cavity.

There would appear to be four possible explanations for this phenomenon. First, perforation of the septum must be considered. However, in Case 3 there is autopsy proof that the catheter had *not* perforated the ventricular septum and there was no clinical reason to believe that this had occurred in either of the other cases.

Second, it is possible that the catheter electrodes were located in the coronary sinus rather than in the right ventricle. This is thought to be most unlikely because

our experience and that of others[2] has been that adequate pacing of the ventricles is difficult to achieve from the coronary sinus unless the milliamperage is increased considerably. Moreover, we have never observed the above-described patterns when the coronary sinus was stimulated.

A third explanation is suggested by the anatomic and septal activation time studies of Sodi-Pallares. He has shown in dogs that the usual delay of an impulse traveling from the left ventricular myocardium across the septum to the right ventricular myocardium is sometimes not encountered in the mid portion of the septum, an area which may be unusually thin. Thus it is possible that our pacemaker electrodes were stimulating areas of the right ventricular septum that were functionally left ventricle, thereby depolarizing the left ventricle first.

Perhaps a more attractive hypothesis is that the impulses may have entered the right bundle branch and then traveled in a retrograde direction to the A-V junction and down the left bundle branch. Anatomically, the upper and lower thirds of the right bundle branch lie subendocardially and adjacent to the right ventricular cavity and therefore could easily be stimulated. Along these lines there is some evidence from the observations of Langendorf and associates[5] that artificial pacemaker stimuli may at times enter the conducting system. They demonstrated enhanced antegrade conduction through the A-V node produced by supernormal phases of conductivity after pacemaker stimulation and postulated the necessity of this stimulus to penetrate the conducting system to the A-V node. Similarly, Burchell[6] observed loss of right bundle branch block when pacemaker stimuli induce a supernormal phase of conductivity in the right bundle.

We believe that the unusual pattern of conduction observed in our fourth case might lend some support to the theory that pacemaker stimuli may penetrate the conducting system of the heart. In this case, the pacemaker stimuli must in some way have affected the conducting system so as to render the right bundle branch and the A-V node refractory, thus only permitting conduction with first-degree block and incomplete right bundle branch block. The possibility that the right bundle branch block pattern was produced by mechanical impingement of the catheter on the right bundle[7] is untenable because the catheter was not moved when the pacemaker was shut off.

The patterns of conduction described in these patients are of more than theoretical interest, since it is apparent that the development of a pattern of right bundle branch block during right ventricular endocardial pacing by a transvenous catheter may not be due to perforation of the septum.

Summary

Four cases showing unusual patterns of conduction produced by pacemaker stimuli are presented. Some of the possible explanations for these phenomena are considered. It is suggested that the pacemaker stimuli in these cases were conducted through specialized conductive tissue rather than preferentially through the myocardial fibers. Thus, the pattern of right bundle branch block occasionally produced by transvenous catheter pacemakers in the right ventricle does not necessarily imply that the catheter has perforated the septum.

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Hemodynamic effects of propranolol in patients with Fallot's tetralogy

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Infants with tetralogy of Fallot are subject to attacks of dyspnea and increasing cyanosis. One possible mechanism of these attacks is an increase in myocardial contractility leading to a decrease in the caliber of the right ventricular outflow tract. Since this area in patients with the tetralogy is often severely narrowed, a further slight reduction in caliber greatly increases the resistance to the passage of blood to the pulmonary artery so that the right-to-left shunt through the ventricular defect and out the aorta increases in magnitude. The suggestion that "spasm" of the right ventricular outflow tract is responsible for some or all of the cyanotic attacks in patients with tetralogy of Fallot has been difficult to prove. Indirect evidence in support of this theory is the observation that the murmur due to pulmonary stenosis is decreased during an attack, presumably due to a further reduction in pulmonary blood flow.[3]

An attack of dyspnea may be precipitated by isoproterenol, which causes increased myocardial contractility but also lowers systemic resistance and increases heart rate and cardiac output.[4] We recently reported that propranolol, a beta adrenergic blocking agent, may be useful in preventing or in treating cyanotic attacks in patients with tetralogy of Fallot. The purpose of the present report is to amplify our previous observations on the hemodynamic changes induced by intravenous propranolol in patients with Fallot's tetralogy.

Methods

Children over 1 year of age were sedated with a mixture of Pethidine, chlorpromazine, and Phenergan. Infants under 1 year of age were given 15 to 30 mg. of phenobarbitone. Determinations of oxygen were obtained with a Waters cuvette oximeter calibrated daily with Astrup pO_2 determinations done on at least one arterial and one venous specimen. The values of oxygen saturation given in this report were mostly obtained from pO_2 determinations done directly by the Astrup technique. Indicator-dilution curves were obtained by injecting indocyanine green dye into the right atrium or right ventricle and sampling blood from the femoral artery through a Waters densitometer with a Harvard motor-driven syringe. In infants who weighed less than 5 kilograms, calibration of the curves with the patient's own blood was not obtained. In larger infants and children, curves were cali

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brated by adding micro amounts of dye to three 5-ml samples of blood. Shunt flow was calculated from the indicator-dilution curves through the use of the formula suggested by Wood for right-to-left shunts.

After control measurements had been obtained, isoproterenol was infused at a rate of 1 to 2 μg per minute for 2 to 3 minutes through the heart catheter and the measurements were repeated. After this propranolol 0.2 to 0.8 mg per kilogram was injected in a single bolus into the right ventricle. The measurements were repeated within 5 to 10 minutes. Following this isoproterenol was again given with the dose increased to 3 μg per minute.

Clinical data

These patients represented the full spectrum of the disease known as Fallot's tetralogy, although the majority did not have severe cyanosis. The ages of the patients studied are provided in Table I; a brief *résumé* of the clinical data follows. J.C. had had attacks of dyspnea, but these had subsided by the time of the study. A.L. was markedly cyanotic at rest but asymptomatic. J.S. and R.S. had had several mild to severe attacks of dyspnea despite their high resting oxygen saturations, and R.S. developed cerebral thrombosis during one attack and this eventually proved to be fatal. K.R. had an associated (small) patent ductus arteriosus and was asymptomatic. N.R. had a predominant left-to-right shunt and was asymptomatic. J.S. and R.T. were asymptomatic at the time of study but both subsequently developed spells of severe cyanosis. The spells in both of these patients have been clinically controlled over a period of 3 months with a total daily dose of 20 mg of propranolol given orally. However, the clinical progress of J.S. is poor and a shunt operation is planned. D.L. and B.H. were older subjects, asymptomatic at rest, who had considerable limitation in exercise tolerance and who have undergone successful open heart repair of their tetralogy subsequent to these studies. D.C. had had spells of severe cyanosis in infancy; these disappeared after a Blalock shunt. However, thrombosis of this shunt occurred and clinical progress was slow. This boy was maintained on oral propranolol 20 mg daily for 2 months. Arterial oxygen saturation as measured at the time of office visits once weekly for 3 control weeks and once weekly for six visits while propranolol was being taken showed a mean increase of 9 percentage points after the beta adrenergic inhibition. Despite this, there was no improvement in his symptoms of weakness and listlessness and a second shunt operation was subsequently performed.

Patient J.M. was the only subject at the time of the study who had a large left-to-right shunt. This was through a Potts anastomosis which had been created when he was 2 years old. Corrective surgery was subsequently carried out. Patient L.T. had severe and frequent attacks of dyspnea (6 per day). After the catheterization study attacks were well controlled on 15 mg of propranolol daily for 1 month. The attacks then returned, although they were less severe and occurred only in the mornings. An aortic pulmonary anastomosis was performed and the attacks have completely subsided.

Results

Data on the patients and the changes in intravascular pressures, arterial oxygen saturation, per cent right-to-left shunt and heart rate are given in Table I. After propranolol, slight decreases were observed in the mean right ventricular systolic and the arterial systolic and diastolic pressures, but these changes were not statistically significant. Increases in systemic oxygen saturation of greater than 10 per cent occurred in 2 patients (A.L. and L.T.). These patients had the lowest initial arterial oxygen saturations. Six subjects showed an increase of 3 to 4 per cent in arterial oxygen saturation, whereas no change occurred in 3 subjects after propranolol. The oxygen saturation in Patient J.M. decreased 6 percentage points after propranolol.

The per cent right-to-left shunt measured from the indicator curves decreased in all subjects. Three subjects showed a change of less than 5 per cent, which is less than the error of the method. However, the change was 10 per cent or greater in

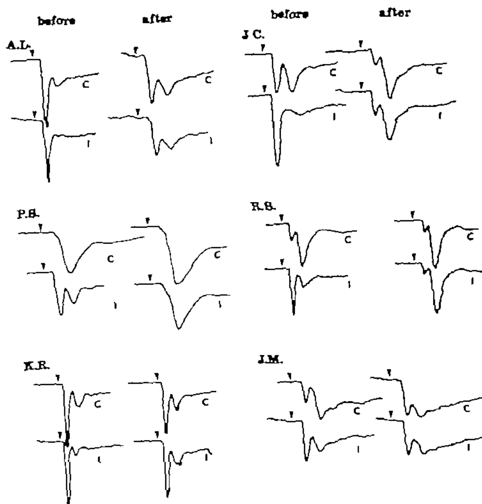


Fig. 1. Indicator-dilution curves before and after propranolol and with isoproterenol in 6 patients. C, Control. I, Isoproterenol. Arrows indicate injection. Curves after propranolol are also marked C and I for the control curve *after* propranolol, and the curve obtained when isoproterenol was given again after the beta-adrenergic inhibition.

the other 10 subjects. The mean shunt before propranolol was 3 per cent and afterward it was 23 per cent. The largest decreases in the magnitude of the right-to-left shunts after propranolol occurred in Patients A.L. and L.T., the patients who showed the largest increases in arterial oxygen saturation. After the propranolol the resting heart rate decreased in 10 subjects, was unchanged in 1, and increased 3 beats per minute in 2 subjects. The mean change for the entire group was a fall in rate of 8 beats per minute.

The pulmonary artery was successfully entered both before and after propranolol in only 2 patients. Fig. 3 shows the pressure withdrawal curve from the pulmonary artery to the infundibulum to the right ventricle in Patient R.T. Extrasystoles occurred in each instance. (In our experience propranolol has not produced any obvious decrease in the irritability of the heart due to mechanical stimulation by the heart catheter.) The pressure curves demonstrate primarily a subvalvular stenosis, and the peak gradient was reduced from 60 to 31 mm.Hg by the propranolol. The elevation of pulmonary arterial pressure after propranolol suggests that the caliber of the right ventricular outflow tract

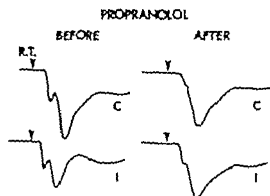


Fig. 2. Indicator-dilution curves in Patient R. T. before and after beta-adrenergic inhibition. Curves after isoproterenol are also shown. Right-to-left shunt reduced from 28 per cent before propranolol to 7 per cent after.

had increased. The indicator-dilution curves did not suggest any marked change in pulmonary blood flow (Fig. 2) and the mean left atrial pressure measured after the catheter had traversed the patent foramen ovale increased by only 1.0 mm Hg after propranolol. In D.L., pulmonary arterial and right ventricular pressures were also obtained both before and after propranolol and the peak gradient was decreased by 17 mm Hg after propranolol. Left atrial pressures were not obtained in this patient. A decrease in peak gradient might also be explained by a change in the time relationships of ventricular ejection or by an increase in pulmonary arteriolar resistance.

Serial film biplane selective angiocardiograms were obtained before and after propranolol in 3 subjects. An interpretation of changes in the caliber of the right ventricular outflow tract on the basis of angiocardiography is difficult because any change would be expected to be minimal and in addition the same phase of systole must be used for comparison in a series of beats when ventricular extrasystoles have not been produced by the injection of the opaque media. Fig. 4 shows the lateral angiocardiograms from Patient J. C. at the same phase of systole recorded in the electrocardiogram and in the absence of any extrasystoles. The caliber of the right ventricular outflow tract appears to have been increased by propranolol. In the other 2 subjects in whom angiocardiograms were obtained before and after

Table 1

Patient	Age (yr.)	Weight (Kg.)	Propranolol dose (mg.)	Pressures (mm. Hg): Right ventricle C	Right ventricle P	Arterial C	Arterial P
J.C.	2	11.5	2.5	95/8	100/15	110/57	115/65
A.L.	2	9.9	1.5	92/9	84/9	115/52	100/37
P.S.	9/12	8.8	1.8	82/7	90/8	90/55	100/57
R.S.	2	12.4	2.5	90/8	98/11	97/67	100/65
K.R.	1	8.0	2.0	105/14	98/10	105/47	105/55
N.R.	3/12	5.3	1.1	92/6	74/8	98/52	77/42
J.S.	3/12	3.1	1.0	90/9	72/13	120/50	83/35
R.T.	8/12	7.3	2.0	80/7	74/8	90/55	90/45
L.T.	6/12	3.2	1.5	100/25	95/20	110/40	105/60
D.L.	8	27.2	5.0	100/8	90/10	118/63	105/50
B.H.	8	20.5	5.0	101/10	92/8	105/60	105/65
D.C.	4	11.3	4.5	105/10	102/10	118/60	115/57
J.M.	12	41.5	5.0	115/13	117/14	151/65	140/60
Means		13.1	2.8	97/11	91/11	110/56	103/53

C, Control. I, Isoproterenol. P, Propranolol. P+I, Isoproterenol after propranolol. Δ, Mean increase in patients tested.

propranolol there was an increased opacification of the pulmonary artery and a reduced opacification of the aorta suggesting a reduction in the right to-left shunt. The presence of extrasystoles during the filming of these angiocardiograms prevented detailed anatomic comparison of the outflow tract areas, and may also have altered the shunt.

The indicator-dilution curves of Patient L.T shown in Fig 5 are of particular interest, in that the initial curve was obtained during an attack of severe cyanosis. Almost no pulmonary blood flow was detected in the curve. The sharpness of the curve suggests that cardiac output may have been elevated Propranolol was given after control measurements had been obtained but the attack was not relieved for 20 minutes. After the attack had subsided the indicator-dilution curves showed a large secondary deflection due to pulmonary blood flow Some of the data from this patient were included in a previous report and it was noted that the patient had severe hypocapnia and metabolic acidosis during the attack, with subsequent improvement.

The marked changes produced by isoproterenol in the contour of the indicator dilution curves is indicated in Figs. 1 and 2 and were similar to those previously reported[3] from this laboratory In contrast after beta-adrenergic inhibition isoproterenol did not alter the contour of the indicator-dilution curves. Before propranolol the isoproterenol produced a mean increase in the heart rate of 48 beats per minute, compared to that after propranolol of only 1 beat per minute. Before propranolol the mean right to-left shunt was increased from 30 to 49 per cent with isoproterenol whereas after propranolol the isoproterenol produced a mean increase of only 2 per cent in the magnitude of the right to-left shunts. This inhibition of the changes produced by isoproterenol confirmed that an effective beta adrenergic receptor inhibition had been produced by the propranolol in the doses used

Discussion

The results of this study give hemodynamic support to our clinical observation that propranolol may be useful in the treatment and prevention of attacks of dyspnea

Arterial oxygen saturation (%)		*% Right-to-left shunt*				*Heart rate (beat/min.)*			
C	*P*	*C*	*I*	*P*	*P + I*	*C*	*I*	*P*	*P + I*
88	92	26	40	13	17	116	163	99	102
54	71	47	59	30	27	135	174	120	120
88	89	5	37	3	6	118	138	117	114
87	88	16	49	13	9	103	159	103	102
76	76	42	63	32	34	108	177	111	114
89	89	26	48	6	9	120	189	117	123
65	63	26	37	23	23	186	195	153	153
70	74	28	20	7	13	93	114	90	90
46	76	31	—	44	—	174	—	165	—
83	87	27	—	19	—	75	—	66	—
83	86	45	78	34	39	81	160	69	72
77	80	46	—	43	—	103	—	93	—
78	72	42	63	32	34	108	177	111	114
76	80	35	Δ19	23	Δ2	117	Δ48	109	Δ1

or cyanosis that occur in patients with Fallot's tetralogy. Singh and Cotsman have also reported on the beneficial effects of beta adrenergic inhibition in the treatment of cyanotic spells of Fallot's tetralogy. These authors demonstrated by phonocardiography that the intensity of the systolic murmur of pulmonary stenosis was decreased during a cyanotic spell and was increased by giving pronethalol. It was suggested that spasm of the right ventricular outflow tract had increased the right-to-left shunt, which decreased the flow through the stenotic area and accordingly the stenotic murmur. Administration of pronethalol slowed the heart and produced an increase in the murmur suggesting an increase in the pulmonary blood flow. Direct evidence of this has been obtained in our Patient

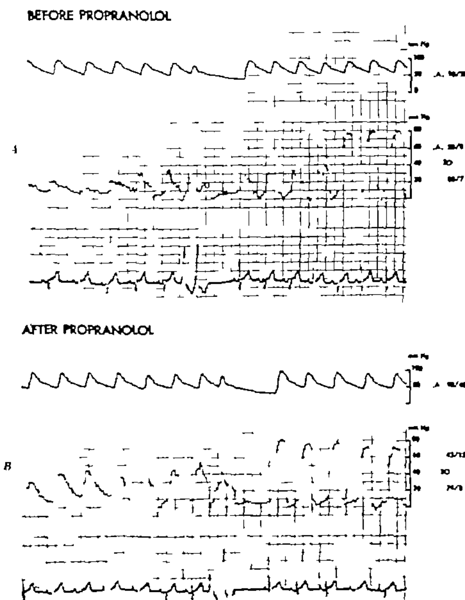


Fig. 3. Pressure curves in Patient R.T. A, Before drugs. B, After propranolol. Pulmonary arterial and infundibular pressures increased after the propranolol.



Fig 4 Lateral angiocardiograms *Left* Before propranolol. *Right* After propranolol. Both films were obtained in the middle of the downslope of the T of simultaneously recorded electrocardiogram. There is an apparent widening of the outflow tract of the right ventricle in the angiocardiogram on the right.

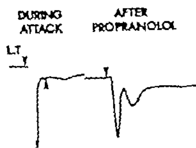


Fig 5 Indicator-dilution curves in Patient L.T at the age of 6 months, during an attack of cyanosis and 20 minutes after the attack had been treated with propranolol. The curve on the left shows rapid circulation with almost no pulmonary flow. A possible peak for the pulmonary flow is indicated by the arrow. The curve on the right, after the attack had ceased, still shows large right-to-left shunt but there now is a large deflection from pulmonary blood flow.

L.T in whom indicator-dilution curves recorded during an attack showed little or no pulmonary flow and after relief of the attack with propranolol the pulmonary flow was definitely increased.

We have attempted to show that propranolol increases the caliber of the right ventricular outflow tract. Angiocardiographic studies have shown suggestive evidence of this in at least one patient. In 2 patients pressure curve studies have also shown a decrease in the right ventricle to-pulmonary-artery peak gradient. Definite evidence of a decreased right-to-left shunt after beta-adrenergic inhibition was obtained by indicator-dilution curve studies in at least 10 of the 13 patients studied although the changes in some subjects were small.

We have proved the effectiveness of the beta adrenergic inhibition by giving isoproterenol before and after propranolol. Before the beta-adrenergic inhibition isoproterenol caused a marked increase in heart rate and in the right to-left shunt and these changes were abolished by propranolol. In a previous study we briefly reproduced the clinical manifestations of cyanosis by giving isoproterenol. No attacks were reproduced in this study, possibly because all but one of the subjects had no severe attacks of cyanosis clinically. The only patient who suffered severe attacks of cyanosis, Patient L.T, was not given isoproterenol during the catheterization study.

The decrease in the right to-left shunt measured by indicator-dilution curves was not always accompanied by a correspond ing increase in arterial oxygen saturation In some subjects right ventricular oxygen saturation was reduced by 3 to 7 per cent saturation points by the propranolol. This change accompanied by a reduced cardiac output as has been shown to occur in normal subjects with propranolol[8] would diminish the expected improvement in arterial oxygen saturation Patient J M who had a Potts anastomosis, demon strated a fall in oxygen saturation with propranolol from 78 to 72 per cent yet the right to-left shunt was decreased from 42 to 32 per cent However right ventricu lar oxygen saturation was reduced from 60 to 46 per cent and the flow through the systemic to-pulmonary anastomosis may also have been reduced

The results we have obtained with propranolol in our older patients are some-what similar to the resting changes re-ported by Honey and associates with the beta adrenergic inhibitor pronethalol in older patients with tetralogy Those au thors found only small changes in resting hemodynamics but did find that pro-nethalol prevented some of the fall in oxygen saturation that occurs with exer cise The suggested mechanism was that exercise may lead to some increase in contractility of the right ventricular out flow tract which is prevented by beta adrenergic inhibition

Young patients with tetralogy of Fallot are subject to attacks of cyanosis of un certain pathogenesis. Pharmacologic stud ies from this laboratory have shown that the right to-left shunt in tetralogy of Fallot can be increased by isoproterenol or amyl nitrite[7] and reduced by angioten-sin Direct evidence that the attacks of cyanosis are associated with a marked increase in the right to-left shunt was obtained in Patient L.T and this would suggest that measures to reduce the right to-left shunt should be of benefit in treating these attacks of cyanosis. This patient was given propranolol intravenously dur ing seven separate attacks on the ward and prompt relief of the dyspnea cyanosis and restlessness occurred in four of the seven attacks.

Summary

Propranolol was given to 13 patients with tetralogy of Fallot in order to study the effects of beta-adrenergic inhibition A decrease in the percentage of right to-left shunting was observed in all patients. The most marked change occurred in one patient studied during an attack of cya nosis. Additional evidence indicating re-laxation of the right ventricular outflow tract after beta adrenergic inhibition was obtained A reduction in the pulmonary artery to-right ventricle gradient occurred in 2 patients and angiocardiographic evi dence suggested an increase in the caliber of the right ventricular outflow tract in one patient These changes produced by propranolol may prove to be of value in the management of the spells of cyanosis that occur in infants with Fallot's tetra logy but a long term study is still required The long term clinical results to date have been disappointing

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Mechanism of cardiac valvular fusion and stenosis

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This report deals with the mechanisms of valvular fusion and stenosis and is based on transitions and early lesions actually encountered; no attempt was made to determine the statistical incidence of any of the intermediary stages. The mechanisms involved in the fusion and thickening are similar to those that occur in the organization of nonbacterial thrombotic vegetations (NBTE). Histoenzymatic techniques have proved to be helpful in a better understanding of NBTE[1]; these techniques have, therefore, been applied in this study.

Fusion at the valvular commissure with thickening of the valve and chordae tendineae are generally considered to be morphologic criteria of rheumatic heart disease. However, such valvular distortion may not be due to rheumatic fever but often actually follows as a result of organization of NBTE, particularly in the region of commissures. Nonspecific aspects of infection and other nonspecific factors such as stress[2-4] also play a part. In stenosis, neither the separate contribution of fibrotic agglutination of approximated valve surfaces at the commissures nor the individual role of interstitial valvulitis has as yet been determined with any degree of accuracy; each factor probably varies in diviually in each instance. Fusion of the commissures is commonly encountered in sclerotic aortic heart valves of aged subjects and may also be superimposed after an interval of many years on heart valves long after any rheumatic activity. The transitional sequences in the incorporation of single and apposed chordae tendineae in stenotic atrioventricular valves have not yet been clearly demonstrated. The development of stenosis long after all rheumatic activity has ceased can be understood on the basis of the superimposed nonspecific mechanism described.

Methods and materials

Forty-five autopsy cases, ranging from a newborn baby to a 92 year-old subject, were selected for this study; in most of these there was fusion at the aortic commissures (30 cases) and at the atrioventricular valves with and without involvement of regional chordae tendineae (10 cases). Many valves with no obvious fusion were also studied, and a few were studied histochemically (5 cases). Tables I and II show the age distribution and the basic diseases, respectively, in the human material. Experimental material studied included 5 dogs (after atriovenous shunt) and 30 rats (10 rats on a high-salt diet,* 10 rats on an atherogenic diet,† 5 rats given endotoxin,‡ and 5 rats subjected to

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*High salt diet = 1 per cent NaCl in Purina chow (General Biochemicals, Chagrin Falls, Ohio).
†Atherogenic diet = Purina chow blended with 3 per cent cholesterol, 2 per cent cholic acid, and 0.3 per cent thiouracil (General Biochemicals, Chagrin Falls, Ohio).
‡Endotoxin = *Escherichia coli*. A WRR (Venereal Disease Experimental) Laboratory, Chapel Hill, N.C.

Table I Age incidence of autopsy cases (45 cases)

Under 10	7
20 to 40 y	4
41 to 60	13
61 to 80	18
Over 81	3

Table II Basic entity in autopsy cases (45 cases)

Malignant tumor	10
Rheumatic heart disease (old)	7
Atherosclerotic heart disease (with myocardial infarction)	4
Myocardial infarction	3
Cerebral vascular accident	2
Lupus erythematosus	2
Pneumonia	3
Myeloma	2
Gastrointestinal bleeding	2
Nephropathy (diabetes)	2
Newborn babies	3
Miscellaneous (arthritis, cirrhosis, gunshot)	3

adrenalectomy combined with 3 days of exposure to cold).

Histoenzymatic techniques were used on 10 distorted and 5 normal valves from human hearts and on the valves of 2 dogs and 5 rats with edema only. The heart valves of these human and dog cases were fixed overnight with Baker's buffered cold formalin. Then transverse sections through the fused commissures were prepared for frozen sections and histoenzymatic reactions. Transverse cryostat sections through the aortic commissures were also prepared from experimental rats, and these sections were fixed in Baker's buffered cold formalin for 20 minutes prior to the histoenzymatic reaction. The following histoenzymatic reactions were performed: reduced diphosphopyridine nucleotide diaphorase (DPNH diaphorase) utilizing Nitro BT after Novikoff[6] adenosine monophosphatase (AMPase), adenosine diphosphatase (ADPase) and adenosine triphosphatase (ATPase) by Wachstein and Meisel[7] alkaline phosphatase by Gomori.

Transverse sections of the region of the commissures studied were also prepared for paraffin embedding in the usual manner and the following routine staining procedures were used: hematoxylin-eosin (H&E), elastica van Gieson, periodic acid Schiff (PAS)–Alcian blue combined stain and phosphotungstic acid hematoxylin of Mallory (PTAH) stain.

Observations

A. Dog and rat hearts. The detailed findings in the experimental groups have been given elsewhere; the main object in this paper is to stress the qualitative developmental aspects of the valvular distortions rather than their statistical incidences. The groups of rats subjected to the adrenalectomy and cold stress and to the administration of endotoxin developed a high incidence of severe valvular lesions. In the high-salt-diet group only edema and thickening were present and in the atherogenic-diet group the accumulation of foam cells and atheromatous plaque were seen at the edge and anterior cusp of the mitral valve where edema appeared with stress in other groups.

Fusion was rarely seen at the aortic commissure in rats and dogs, except that an old dog occasionally showed such fusion (Fig. 1). *In the region of the commissure* there was a goodly amount of ground substance and this was affected by stress and tended to show marked edema (Fig. 2); the interstitial edema was more prominent at this site than at the edge of the valve. Although no definitive fibrotic fusion was found in the rats of this series, the region of commissures often showed edema. Such an edematous area was strongly positive with Alcian blue. The surface endothelium was rather loosely attached at the edematous region (Fig. 2). In the rat, the chordae tendineae were also prone to react with edematous swelling to nonspecific stress or infection. Such areas of involved chordae tendineae and valve showing interstitial edema and cellular reaction do become approximated and this can then lead to fusion (Fig. 3); this was particularly true for fusion of an altered chorda with the



Fig. 1



Fig. 2



Fig. 3

Fig. *1* Aortic valve from an old dog 16 months after femoral arteriovenous shunt. The cusps are thickened and edematous. Nodules are present at the commissures (*arrows*), with commissural fusion.

Fig. *2* Microscopic photograph from 7-year-old dog, 5 months after a femoral arteriovenous shunt. The spongiosa at the commissure of both cusps shows marked edema with some cellular reaction toward the surface (*arrow*). Hematoxylin-eosin, ×40.

Fig. *3* Mitral valve with insert of chorda tendina from rat subjected to bilateral adrenalectomy and 3 days of exposure to cold. The chorda (*long arrow*) shows marked edema and moderate cellularity. The edge of valve is also edematous with cellular reaction (*short arrows*). The chorda and valve might be ready to fuse. Hematoxylin-eosin, × 120.



Fig. 4. A fresh vegetation (arrow) is superimposed on the aortic valve in a 49-year-old woman who died of lupus erythematosus. The dark-stained area corresponding to the corpora arantii represent some [illegible] which were positive for amyloid (Lugol test).

Fig. 4A. Photomicrograph of a transverse section of Fig. 4 in the region of the commissure (C), demonstrating old fibrotic and fresh vegetations (arrow). The fresh vegetations (arrows) are superimposed on the underlying older fibrotic healed vegetation. Hematoxylin-eosin ×15.

Fig. 5. A 56-year-old man with long-standing rheumatic heart disease. An [illegible] fusion is present and granular nonrheumatic NBTE (arrow) are superimposed.

free edge of the cusp of a similarly distorted mitral or tricuspid valve.

Histoenzymatic studies revealed the AMPase reaction to be rich at the surface of the valve and in the valve proper and to be particularly prominent in areas of edema. The ATPase and ADPase reactions were positive in the endothelium

B Human hearts The aortic commissures of the newborn baby or young subjects tended to show edema and here too fusion was rarely present. In adults fusion was more common and more evident with age. Various types and different degrees of fusion were encountered from that of a relatively fresh nonbacterial thrombotic vegetation (NBTE) at the commissure (Figs. 4 and 4A) to a bandlike membranous bridge, to a more rounded organizing mass located between the leaflets. All usually result in a limitation of movability Then there was also a further tendency of additional increments of superimposed NBTE to occur on the sites of fused commissures (Fig 5 *arrow*) Histologically focal cellular reaction was often present on the ventricular aspect (spongiosa) of the valve. A nodular healing thrombotic vegetation was more often present without complete fusion On occasion, fibrinoid material filled the commissure. The leaflet often showed collagen changes, and a thrombus was present in between the leaflets, or there was a superimposed vegetation on a nodular older vegetation (*arrow* Fig 4A)

The histoenzymatic reactions at the fused aortic commissure revealed the same features as those found in ordinary NBTE on the valve i.e. the DPNH-diaphorase reaction revealed formazan precipitation on the surface (Fig 6B *arrows*) and in the reactive cellular elements (Fig 6B *arrowhead*) at the base of such a vegetation The AMPase reaction was positive toward the surface of the older vegetation at the base of fresher vegetation (Fig 6C) The ATPase (Fig 6D) and ADPase reactions were weak at the surface of the older vegetation and both were strongly positive in its depth

The same structural pattern and enzymatic reactions were found in regions of fusion between the chordae and valve or between the chordae tendineae and ventricular or atrial endocardium This was best demonstrated by the DPNH-diaphorase reaction (Fig 7) The arrow in Fig 7 points to a superimposed fresh platelet vegetation on an older vegetation located on the surface of the chorda tendina, and an active reaction of fibroblasts is seen surrounding the older vegetation The transformation of the recurrent NBTE vegetations can thus lead to fusion between the chordae tendineae Thus the fusion between the adjacent chordae tendineae appeared to have the same mechanism as does the commissural fusion

The following case demonstrates well the mechanism of fusion. A 78-year-old woman who had had arthritis was treated with gold triamcinolone for 4 months. She was hospitalized with a fever of 103 F., and the culture from the throat revealed nonhemolytic streptococci. The blood culture positive at first, became sterile after massive antibiotic therapy At autopsy bronchopneumonia was found and postmortem culture of lung showed *Staphylococcus aureus* coagulase-positive The mitral valve showed only some sclerotic changes. However grossly several chordae tendineae showed swelling with minute areas of granularity and fresh fusion (Fig 8) A cross section of the granular area of the chordae tendineae revealed a few vegetations on the surface with a cellular reaction at the base of the vegetations. The DPNH-diaphorase reaction on a consecutive microscopic section (Fig 8A *arrows*) showed fresher platelets in the outer layer of the nodular organizing vegetations with the active cellular reaction at the base. Another deeply placed nodule was present, surrounded by reacting cells (Fig 8A *lower right large arrow*) This latter buried nodule seemed to be of the same structure as the nodules on the surface but the organization was more advanced The alkaline-phosphatase reaction was positive at the base of the vegetation in the chordae tendineae (Fig 8B *arrows*) The positive alkaline-phosphatase reaction in the reacting cells at the base of vegatation suggested a previous bacterial contamination A longitudinal section of the chordae tendineae also demonstrated nodular vegetations of different

Aristocort, Lederle Labs., Pearl River N Y



Fig. 6. A-D are consecutive frozen sections from a 70-year-old man who suffered from lymphoma. Grossly there was no evidence of rheumatic heart disease but fusion of the aortic commissure was present and fresher vegetations were superimposed on the older vegetations. *B*, *C*, and *D* are higher magnifications of the boxed area [illegible] with enzymatic reaction [illegible] material [illegible] present at the top of the zone of fusion and between the cusps (*arrows*). [illegible] Older organizing vegetation [illegible] cusps. Hematoxylin-eosin, ×25. *B*, DPNH diaphorase reaction demonstrates [illegible] the reacting cells (*arrowhead*) in the zone beneath the fresher vegetation (*Vg*), corresponding to boxed area [illegible] The [illegible] superficial layer of platelets on the surface. Magnification ×100. (*For sections C and D see page 43.*)

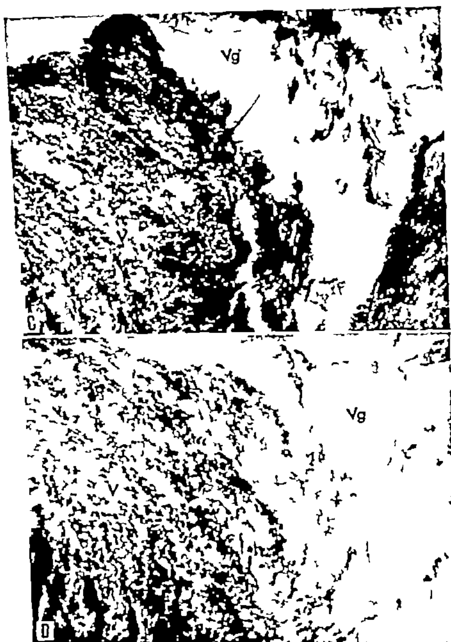


Fig. 6—Cont'd. C, AMPase reaction reveals positive reaction product toward the surface of the organizing vegetation (V), at the base of the fresher vegetation (Vg). This reaction is most prominent at the surface of the organizing older vegetation (V) and diminishes deeper in. Magnification, ×100. D, ATPase reaction. The base of the fresher vegetation (Vg) reveals negligible reaction only, but there is more positive reaction seen in the depth corresponding to the older vegetation (V), where the AMPase reaction (C) is diminished. Magnification, ×100.



Fig 7 A microphotograph from 60-year-old man with old rheumatic heart disease and rectal carcinoma The chorda tendina ppears in the upper part of the photograph and the entricular endocardium is t the bottom. A different and lder phase of the egetation (v) is present between the chorda tendina and the endocardium. A fresh platelet vegetation (rrow) is superimposed on the older egetation A organizing process is evident in the older vegetation DPNH-diaphorase reaction X110



Fig 8 Enlarged gross picture of the mitral valv from 78-year-old woman showing thicken g and edema t the edge of valv with obvious f lon of chordae tendineae Granular ppearance of chordae ith veget tions (rrows) is present Magnification X6 (For F g 8 I C ee page 45)

ages (Fig 8C) The centers of the vegetations were more homogeneous in hematoxylin-eosin staining In Fig 8C above such a central homogeneous zone there were some platelet rich areas dark and granular with DPNH-diaphorase reaction

Comment

Duguid[11] emphasized the significance of the surface deposit of fibrin Tweedy[12] and Magarey also stressed this contribution to valvular thickening and the formation of Lambl s excrescences. The results of this study confirmed their view but the more frequent factor found wa that of platelet vegetations often with minimal fibrin also new NBTE were often superimposed on an older vegetation Such vegetations in the form of superimposed layers were present in the region of com

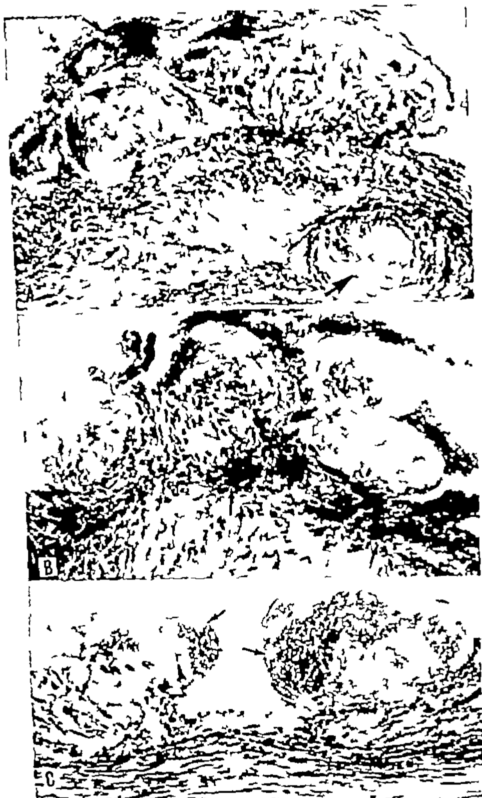


Fig 8—Cont d *A* nd *B* Cross sections of single chorda with the granular surface. *C* Longitudinal section of same *A* Fresh platelet areas ppear at the top (*long arrows*) and in the egetation (*short arrow at left*) The egetations show an organizing process. One nodule is seen t the lower right (*large arrow*) surrounded by cells. This nod le seems to be an organized egetation similar t the nodular fresher vegetations t the surface DPNH diaphorase reaction, ×180. *B* The alkaline phosphatase reaction show positive-reaction product in the reacting cells focally (*rrows*) t the base of vegetation ×180 *C*, DPNH-diaphorase reaction A longitudinal section of the chorda with granular ppearance show different stages of formation of egetation, i.e. platelets of different age. Fresh platelet vegetations (*rrows*) are superimposed on older vegetation ×180

missures of the mitral and aortic valves and are not uncommon.[8]

The NBTE vegetations found on the surface of an acellular collagenous valve are quite prone to be torn off. With time such NBTE also are prone to show organization. NBTE on the aortic valves tend to persist and to organize and to calcify, particularly on the commissures, in contrast to the NBTE on the free valvular surface. The Lambl's excrescences or whiskers represent organized NBTE, often with a papilliferous central core; this viewpoint is based on transitional lesions encountered.

The interstitial alterations of the valve and chordae, both in animal and human material, which are represented by edema, fibrous thickening with or without cellular reaction, *and local enzymatic activities*, are apparently related to the development of fusions with and without NBTE. The interstitial valvular reaction and the overlying NBTE do not necessarily parallel each other, although they often do in the experimental lesions.

Osler stressed that in most cases, malignant ulcerative endocarditis (bacterial endocarditis) was prone to develop on the previously damaged heart valve. It has been widely agreed that rheumatic heart disease is the main underlying cause of valvular damage.[14] Abbott[20] and Lewis and Grant emphasized the role of the bicuspid aortic valve, particularly of congenital origin, in bacterial endocarditis. Gross and Friedberg[22] investigated the NBTE and noted that rheumatic heart disease was the main underlying disease associated with this lesion. Grant, Wood, and Jones[23] demonstrated experimentally that in the injured heart valve the platelet vegetation appeared first and then bacterial contamination of the primary platelet vegetation occurred. Recently, *such a mechanism of infection of* a primary NBTE vegetation has been stressed.[24,25]

The results of this study indicate that the intermediary stages in the process of *fusion are the same as the changes found* in the organization of NBTE *on the valve*. No transitional lesions have been encountered which would enable one to reconstruct a graded gross and microscopic sequence from an early active interstitial valvulitis or edema to final fibrotic thickening and stenosis. This should not be construed to imply that such interstitial changes in the valve do not contribute to fusion and thickening to yield classic mitral or aortic stenosis. It is our impression that this is not as common as heretofore assumed and that organization of NBTE in crucial sites in relation to the valves is a more important factor. At least transitional intermediary lesions showing the effects of such organization of NBTE are encountered more frequently. The sequence of thrombosis, organization, and various histochemical changes probably are identical in rheumatic valvulitis, systemic lupus, and NBTE.

Summary and conclusions

Forty-five hearts from human beings, 30 from rats, and 5 from dogs were subjected to the study of the sequences of aortic commissural fusion. Such fusion between contiguous valve surfaces and chordae tendineae and between the apposed adjacent chordae tendineae of atrioventricular valves was also studied. The sequences of fusion were found to be the same as the changes which occur in the organization of ordinary nonbacterial thrombotic valvular vegetations (NBTE). Histoenzymatic reactions were used to clarify the sequences encountered. The relative importance of the healing fibrosis involving NBTE in relation to the contribution of concomitant interstitial valvulitis was discussed.

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Experimental and laboratory reports

The true venous pulse wave, central and peripheral

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The recording of the jugular phlebogram (JP) or venous pulse is a classic technique that has been employed for over half a century for the study of disordered heart action. This has been extensively described in monographs by Mackenzie,[1] Lewis, and Groedel. The records obtained are a composite montage of pulsations from arterial and venous sources, and it is, strictly speaking, a misnomer to call these records phlebograms or venous pulses. However, the clinical value of the recording of the jugular phlebogram is well established. Lewis has commented on this: "There are no forms of irregular heart action which may not be identified by this method." Mackenzie[1] recognized that if the arterial wave could be subtracted from the jugular phlebogram we would have what he called "the true venous pulse wave." Reference to the review on this subject by Bachmann[4] illustrates the confusion in regard to the identification of the mechanisms involved in the production of the component waves of the jugular phlebogram. For example, seven factors are quoted as being involved in the production of the v wave; this author, however, adds to the confusion by stating that the v wave is in fact two separate waves. The origin of the c wave is also questioned, and it appears that the only consensus of opinion is that in regard to the atrial origin of the a wave. It would thus be of value to devise a means of resolving these conflicts and clearly identifying the origin of these waves.

An important point which remains to be examined is the influence that the associated waves have upon the recorded contours of each other in these composite recordings. Thus, although it is generally accepted that the a wave is of venous origin, the underlying arterial pulse in late diastole may affect not only its shape but also its timing. Another neglected aspect of phlebography which merits attention is the mechanism involved in the formation of the negative waves. Since this and many other problems cannot be studied satisfactorily until we are able to have a "true venous pulse wave" record, it was considered that the devising of a means for recording indirectly the central "true venous pulse wave" would be of value.

The indirect study of peripheral venous pulsations appears to have been neglected, although direct recordings were made by Cauer[7] and by Pederson from venipuncture. A study of the behavior of the peripheral venous volume pulse was considered to be of value since it might provide some information in regard to the problems related to venous stasis and resistance to flow in the peripheral veins

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during the various phases of the cardiac cycle.

The prime purpose of this paper is to describe techniques for the recording of the "true venous pulse" at a central site and at a peripheral site and thereby improve this indirect approach to the study of some of the dynamic events of right heart activity. The nomenclature of "true venous pulse" is adopted here as it was introduced by Mackenzie.

The apparatus

The apparatus is presented diagrammatically in Fig. 1. Instead of the usual metal cups 1 inch air-filled rubber balloons were used. These balloons are backed with adhesive tape and fixed to plastic strapping (see Mackay and Walker[8]). The pneumatic systems for recording the two sets of pulsations are kept separate, and are connected to water manometers and reservoirs whereby the pressures can, with hand pumps, be set and maintained at desired levels. In the tube between the 5-liter pressure reservoirs and the recording system a fine needle (gauge 25) is inserted which keeps the pressure in the recording balloons and transducers constant but allows the configurations of the volume pulse waves to be faithfully recorded. This system acts as a self-centering device. Rigid walled plastic tubing is employed throughout the systems. Since the carotid pulsations are usually of a larger amplitude than the arterial pulsations in the jugular phlebogram, a cylinder whose capacity can be varied from 10 to 500 c.c. is inserted into the carotid recording system in order to reduce and match the magnitude of the pulsations from the two sites.

The insertion of tubes and cylinders into the recording systems reduces the amplitude of the recorded waves but does not significantly affect the frequency response of the system, and the significant waves are unaffected. The frequency response of these systems was adequate for the purposes of recording the significant pulses.

The recording gauges were matched Statham strain gauges (P 23H No. 113) by means of which it was possible to record two sets of pulsations and obtain a third record of a "differential" tracing by the subtraction of the carotid pulsations from those recorded from the jugular phlebogram site.

A four-channel Grass polygraph was

Fig. 1. Diagrammatic representation of one of the procedures devised for the recording of the "true venous pulse." *C* is the site for recording the pulsations from the carotid artery. *JP* is the site for recording the jugular phlebogram. The cylinder has a variable capacity of 10 to 500 c.c. The transducer is by Statham (Puerto Rico—P 23H No. 113) and is used to differentially subtract the arterial (*C*) from the arterial plus venous pulsations (*JP*), giving the differential record of the "true venous pulse" (*TVP*). The polygraph is by Grass; the reservoir has a capacity of approximately 5 liters and is connected to a water manometer and a pump. Hypodermic needles (gauge 25) are placed in the tubes by which the reservoirs are attached to the recording systems.

employed to record the electrocardiogram, the jugular phlebogram, the carotid pulsations, and the differential record of the subtraction of the carotid pulse wave from the jugular phlebogram. In addition, a Honeywell Visicorder and Tektronix oscilloscope were used. Balancing of pulses was also carried out electronically.

Procedures for recording the central "true venous pulse"

Pulsations are recorded from two sites: (1) that of the carotid artery in the neck (C) close to the angle of the mandible and (2) that at which the classic jugular phlebogram (JP) is recorded in the supraclavicular fossa (see Fig. 1).

The following steps were found to be important in obtaining satisfactory records. With the subject supine, a classic metal cup covered with a rubber membrane was placed over several areas of the neck until suitable records were obtained. By this means the best sites for recording the jugular phlebogram (JP) and the carotid pulsations (C) were selected and marked (see Fig. 1). With the subject upright, the recording balloons were secured in place by plastic strapping and surgical adhesive tape over the point previously marked. Matching the sensitivity of the recording channels was found to be useful. With the Grass polygraph and the matched Statham strain gauges this is feasible and easily achieved. The noncentering bridge 2K of the Grass preamplifiers was used. Thus it was easy not only to judge the timing but also to compare the amplitude of the records. The subject held his breath in a relaxed position with the glottis open during each recording.

The subject was placed in a head-up position, 30 to 50 degrees, so that the records from the carotid and JP sites had a similar arterial configuration and so that no a wave was present in the JP record; the pressure in the two recording systems was set at approximately 4 cm H_2O. The differential record at this stage may have a biphasic appearance because the two recording sites are at different distances from the heart. Temporal alignment was thus necessary and was carried out by adding lengths of tubing to the JP recording system, thus delaying the arrival of its pulse until the anacrotic limbs of the two arterial pulsations were coincident.

The pressure of approximately 4 cm H_2O used in the recording system does not have any significant compressing effect on the veins and does not exert an extravascular transmural pressure of 4 cm. H_2O (see Mackay,[8] Fig. 8). This pressure is used to inflate the balloon so that it will fit the contours of the skin and avoid artifact waves that occur in a semifilled balloon.

The force and amplitude of the carotid pulsation from the carotid site was usually greater than the carotid pulse from the jugular phlebogram site, thus causing a negative monophasic wave in the differential record. This difference was abolished by increasing the capacity of the volume of the cylinder placed in the carotid recording system. Additional balancing may be achieved by varying the pressures in the two recording systems. With this balancing the differential record should have no marked fluctuations (see Fig. 2,B). This part of the balancing procedure may be done electronically (see later).

The recording of the "true venous pulse" (TVP) was done after lowering the subject from the 40-degree head-up position to a head-up position of 5 to 10 degrees, so that a characteristic JP record was obtained from the JP site but at the same time no a wave appeared in the record

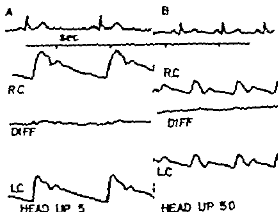


Fig. 2. Record of carotid arterial pulsations. The recording sites were as high as possible on both sides of the neck. *RC*, Right carotid. *LC*, Left carotid. In *B* the subject was tilted 50 degrees head-up; in *A*, 5 degrees head-up.

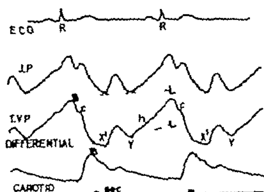


Fig 3 A t pical record of the true venous pulse (TVP) as obtained by the equipment described in Fig 1 The carotid record this instance was taken from the left side The lettering of all the wa es here, as well as ll of the other figures is that adopted for the classic jugular phlebogram (Mackenzie!) Note the hange in the slope of the base line (B-L) from the JP t the TVP

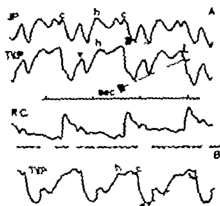


Fig 4 Record showing the ariations that may occur in the records of the true venous pulse I I the right carotid pulse as recorded for the subtraction proced I B the TVP alone is presented.

from the carotid site (C) The differential record now is that of the true venous pulse (see Figs. 3 and 4)

Since the balancing of the two arterial pulsations was carried out with the sul ject in the 40-degree head up position the question arose whether the arterial pulses remain so balanced when the subject is tilted downward Therefore records were obtained from the carotid arteries on both sides with the subject tilted head-up 50 degrees and the pulsations were balanced (see Fig 2 B) The sul ject was now tilted into a 5-degree head up position and the recording was repeated (see Fig ? 1) Note that although the amplitude of the pulsa tions increased twofold these pulsations remained balanced as shown by exami nation of the differential record It was found to be feasible to use the right carotid pulsations for the purpose of differentiation in order to ol tain the true venous pulse

Another way of demonstrating that the arterial components were still balanced when the sul ject was tilted head down ward was that of removing the venous component of the neck pulsations by venous congestion of the four limbs (see Fig 5,A) This procedure was carried out in a heated room in order to promote venous dilatation After temporal align ment and pulse balancing in the 40-degree head up position the subject was then tilted to an approximately 8-degree head-up position and the TVP was recorded Cuff pressures of 80 to 100 mm Hg were applied to the four limbs. After ? to 4 minutes the venous congestion was adequate enough so that the venous component could be removed from the JI and TVP records leaving a differential record matching that recorded in the 40-degree head up position. The release of the congesting cuffs allowed the pulse wave contours of the TVP to return to match those orig nally obtained (see Mackay) These two experiments show that although the arterial pulsations may change in amplitude when the position of the body is changed their balancing is unaffected

A problem which sometimes arose and which occasionally was insoluble was that a marked dissimilarity occurred between the two arterial pulsations from the two recording sites. Usually a balance could be achieved by transferring the carotid record ing site to the same side as that of the jugular recording or by shifting the jugular recording site about three quarters of an inch in a cephalic direction.

A method of construct ng a ecord of the true venous pulse was also devised by subtracting the venous component by means of venous congestion cuffs. The subject is placed supine head up at approximately 8 degrees. The jugular phle

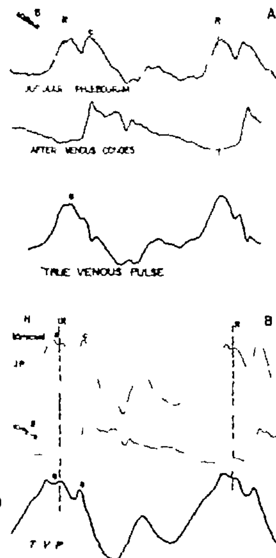


Fig. 5. A, A simple method is demonstrated for the construction of record of the true venous pulse by removing the venous component from the jugular phlebogram by venous congestion of the four limbs. The subject was 8 degrees head-up, and high ambient temperature was employed to cause venodilatation. The middle record shows that after 4 minutes of venous congestion the JP became typical arterial volume pulse. This latter pulse was subtracted from the JP and a constructed "true venous pulse" is obtained (*see lowest record*). The separate records were aligned from the ECG records of similar duration. *B*, The "true venous pulse" was constructed by subtracting records obtained at different angles of tilt. It should be remembered that at different angles of tilt the arterial pulse will vary in magnitude. The "true venous pulse" was obtained *by subtracting the middle* record (arterial pulse) from the top record of the jugular phlebogram. Note the angles of tilt shown in the figure. The configuration of the JP in section A is different from that in *B* because of recording at different angles of tilt.

gram is recorded and then the venous component of the pulsations is removed by means of the venous congesting cuffs on the four limbs at pressures ranging from 80 to 100 mm Hg. The remaining arterial pulse is then arithmetically subtracted from the JP record and the true venous pulse is constructed as in Fig. 5,A. This method has the merit of simplicity since no complicated balancing procedure is involved. In addition the intrinsic arterial pulse from one recording site is used for *the purposes of subtraction. The disad*vantage of the method is that one has to use records obtained at different times and in addition the final record is a laboriously constructed one. A tilting procedure may be used but it should be remembered that the tilting will alter the magnitude of the associated arterial pulse. Such a result is shown in Fig. 5,B. Electronic methods of differentiation will be discussed later.

Procedures for recording the peripheral true venous pulse

The subject is placed supine on a tilt table at 10 degrees head-down, the right arm is supported in a dependent position 5 degrees below the *horizontal* and the left arm is elevated and supported about 35 degrees above the horizontal (see Fig. 6).

Two 1 inch balloons (attached to manometers and reservoirs) are fixed in *position in opposite antecubital fossae* and inflated to about 1 cm H_2O. The record from the left arm will be that of an arterial volume pulse since the veins are collapsed whereas the record from the right will be more complex since it will *in addition contain venous pulsations.*

The main aim of the procedure was again to devise a means for the subtraction of the arterial component from the complex pulse recorded from the right arm and thus provide a true venous volume pulse wave record. The problems involved in this are similar to those involved in the indirect recording of the central "true venous pulse" in the previous procedure.

The balancing procedure can be done with both arms of the subject elevated so that only arterial pulsations are recorded from both limbs or it can be achieved when a venous occluding cuff is applied at 30 mm Hg to the right dependent arm in

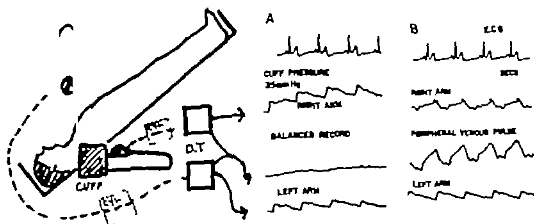


Fig. 6. Diagrammatic illustration of the indirect procedure for obtaining the peripheral "true venous pulse" record. The differential transducer (*DT*) is the same as that in Fig. 1. The variable capacity cylinder (*C.V.L*) was placed in either the right or left system depending on which system had the arterial pulse of greater magnitude. A heated environment was used and the subject was tilted 5 to 10 degrees head-down, with the right arm suspended downward at an angle of about 5 degrees. The arterial records from the left arm (elevated 30 to 40 degrees) were balanced with those from the right arm when a venous occluding cuff was applied to the latter at approximately 35 mm. Hg. Note that no significant fluctuations occur in the differential record (*second from bottom* of *frame A*). Frame *B* demonstrates the recording of the peripheral "true venous pulse." Here there is no pressure in the cuff on the right arm.

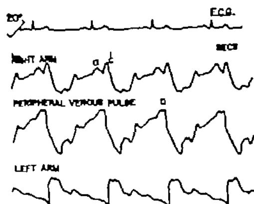


Fig. 7. Records obtained by a procedure similar to that described in Fig. 6. However, the angle of tilt in this case was 20 degrees head-down. *Peripheral venous pulse* is a record of the peripheral "true venous pulse."

order to occlude the venous pulsations. Fig. 6,*A* and *B* presents records obtained after such a procedure. It will be noted that the *differential* record in Fig. 6,*A* shows few significant pulsations. Removal of the pressure in the venous occluding cuff on the right arm permits the addition of the venous pulsations, which now appear in the differential record (see Fig. 7). Balancing the records from the arm pulsations presented fewer difficulties than did balancing those from the neck.

It has already been demonstrated (MacKay[19]) that the application of the subdiastolic cuff pressures used here does not affect the volume pulses in the arm. An explanation is given by Mackay.[11]

Results

The results from the recording of the central "true venous pulse" are presented in Figs. 3 and 4.

A comparison was made in a series of 7 subjects between the central "true venous pulse" recorded before operation and the pressure waves recorded from the right atrium by means of the short catheter that the anesthetist uses to record central venous pressure. A typical comparison is shown in Fig. 8.

The results from the indirect recording of the *peripheral* "true venous pulse" are set out graphically in Figs. 7, 10, and 11. Fig. 7 shows an enlarged record of a typical venous pulse after the balancing procedure. Figs. 9 and 10 show a series of the differentially recorded venous pulses with the

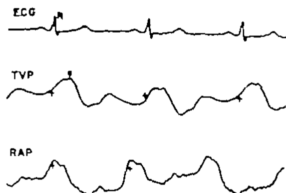


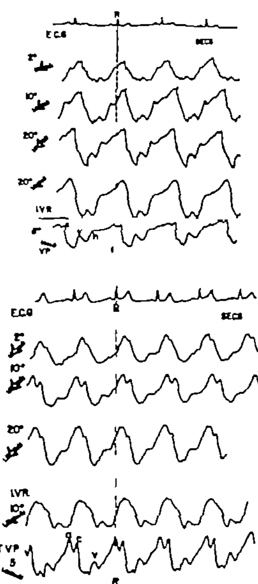
Fig. 8. Typical record of the central true venous pulse (*TVP*) and right atrial pressure (*RAP*) in the same subject. The plus signs denote the timing of the R waves of the ECG. The records were obtained at different times. The record of the RAP was obtained from the short venous catheter used continuously by the anesthetist to measure right atrial pressure.

subject tilted at various angles. They are compared with an intravenous record (IVR) and a record of a true venous pulse (TVP) recorded centrally.

A simple way to physiologically dissect the various components of the complex arm pulse wave is shown in Fig. 11, wherein venous occlusion resulted in an arterial wave but digital compression of the subclavian artery resulted in a typical true venous pulse. (In this instance digital occlusion of the artery during venous compression with the pressure cuff obliterated all pulsations.) Subtraction arithmetically gives contours of venous pulsations similar to those obtained experimentally.

For comparison, records were made intravenously from the antecubital vein. Typical records are shown in Figs. 9 and 10.

One problem with intravenous records is that arterial pulsations are often transmitted to the vein so that for comparison intravenous records were only used from those subjects in whom this arterial pulse was not transmitted. The intrusion of an arterial pulsation from the neighboring artery into an intravenous record can be demonstrated by applying a venous compression cuff above the intravenous needle, in which case the residual arterial pulsation, if present, will be observed.



Figs. 9 and 10. These are comparative records on the same subject of the peripheral true venous pulse waves (*upper three records*) and intravenous records (*IVR*) and the central true venous pulse waves (*TVP*).

Electronic recording and differential subtraction are shown in Fig. 12,*A* and *B*. The records were made on a Tektronix oscilloscope. The outputs of the driver amplifiers of the Grass polygraph were used. That from the carotid (whose polarity was reversed) and from the JI sites were connected by the resistance of a variable potentiometer. The movable arm in contact with the resistance was positioned so that a balanced differential record was obtained (see Fig. 12).

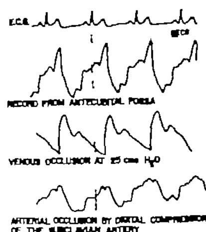


Fig. 11. Illustration of the separation by means of venous occlusion and arterial compression of the venous from the arterial components of a composite indirect record obtained from the antecubital region. When arterial compression was carried out at the same time as venous occlusion, no significant waves were recorded. The lowest record is in effect that of the peripheral "true" venous pulse.

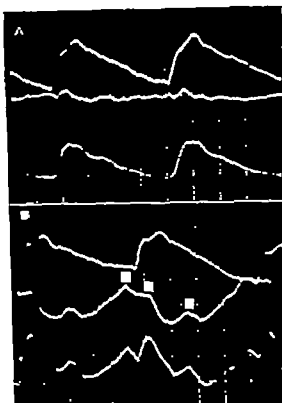


Fig. 12. Records of the peripheral true venous pulse was recorded on a Tektronix oscilloscope after electronic balancing. A presents the balanced record with venous occluding cuff pressure. In B the venous occluding cuff has been removed, and the middle record is that of the peripheral true venous pulse. It should be noted that the size of the records does not represent the voltage of the signals that were used for balancing.

Discussion

The prime purpose of this study was to devise a means whereby the "true venous pulse wave" could be recorded at a central and at a peripheral site. The basic procedure was to record a composite pulse wave of arterial and venous origin and then subtract the arterial component leaving a purely venous wave formation.

Thus the first question which arises is "To what extent do these indirect recordings represent a purely venous function?" To attempt to answer this by measuring atrial and venous pressures is not easy. The measurements of volume and pressure in the venous system are not strictly comparable and depend very much on the variation in the degree of filling of the venous system. When this is only partial marked changes in volume may be associated with small changes in pressure. Thus the indirectly recorded central "true venous pulse" may not be strictly comparable to the pressure waves recorded directly from the right atrium (see Fig. 8); for example, the amplitude of the v wave was usually more marked in the central "true venous pulse" recording. There was a closer similarity between the RAP (right atrial pressure) record and the TVP than between the RAP tracing and the classic jugular phlebogram. The timing of the peaks of the waves of the RAP and TVP were also more comparable. In addition the c waves in the two sets of tracings of the RAP and TVP were similar and much less marked and occurred earlier in systole than the c wave of the JP. In the case of the peripheral venous pulse it should be mentioned that intravenous needles are poor transmitters of changes in intravenous pressure. However, certain similarities do emerge here. There are coincident falls in volume and pressure during ventricular systole, but during the next phase in which the volume and pressure recover, the rise in volume is usually the more rapid (see Figs. 9 and 10). The

closest similarity occurs when the venous pressure is high as when the subject is tilted 20 degrees head-down (see Fig 9)

When one compares the records of the central true venous pulse wave with the classic jugular phlebogram the most obvious difference is that of the c wave. This may be absent (see examples in Fig 4,*A*) If it is present it is small (Fig 4,*B*) and coincident with the early part of the anacrotic limb of the carotid pulsation. It has been generally recognized that the c wave of the JP was due preponderantly to the associated carotid pulse (see Groedel[3]) However it was also recognized that a possibility existed that a part of the c wave was due to a synchronous pulsation of venous origin (from the right side of the heart) Two points remained unclarified first the timing of this component and secondly what proportion of the c wave was arterial and what proportion was venous in origin Mackay[13] had examined this question experimentally in an earlier study and this present method enables us to show that in the "true venous pulse the c wave may be absent, but when present it occurs early in systole This comparison applies to the pulsations recorded at a peripheral site Here the c wave in the composite arm record is more prominent (see Fig 11) than that in the peripheral true venous pulse wave.

One aspect of this problem which appears to have been neglected is the true configuration of the venous pulse wave in diastole From these results it would appear to have a significantly more obvious rising base line (see *B-L* in Figs. 3 and 4)

The v and h waves are superimposed on a more rapidly rising base line which starts at the bottom of the Y[1] wave and rises to the summit of the a wave. The rate of rise in this base line may be of significance when cardiac filling in diastole is under examination

A study of the v wave is warranted Because it is often associated with the coincident dicrotic wave some confusion is likely to arise in regard to its origin From the results here it is obvious that this wave is predominantly of venous origin and a study of its temporal relationship to other cardiac phenomena is more feasible. In many other instances study of the venous pulse is difficult because of abnormalities of the associated arterial pulse. Here we may have a means of solving this problem

Another neglected study is that of the factors involved in the negative waves. Heretofore this has been difficult since the associated arterial pulse has distorted these waves. It will be noted that the negative X wave is more prominent with a rapidly descending slope from the summit of the a wave than in the classic JP

Comparison of the peripheral true venous pulse volume record with that of the central true venous pulse is of interest It might be assumed that the characteristic waves result from similar basic mechanisms in both instances. The central records present more marked fluctuations which as might be expected are smoothed out at the more distal recording site otherwise an over all similarity is found

It is interesting to speculate on the factors involved in the formation of these peripheral venous pulse waves It should first be emphasized that the recording elements only register changes in volume When the phasic changes in arterial volume have been subtracted the residual venous volume record (true venous pulse wave) will show fluctuations due to the variations in the central resistance to venous outflow from the limb It should be remembered that the *peripheral* venous filling is non phasic since the blood has passed through the resistance vessels and enters the veins in a steady flow When the resistance to the central outflow from the limb is high and thus the peripheral filling exceeds the drainage rate the venous volume may increase rapidly this volume will extend centrifugally along the veins and a positive pulse wave will be recorded Since the direction of the blood flow and filling is from the peripheral part of the vein the valves will not affect the formation of this positive pulse wave because this centrifugal filling does not imply a backflow If however the central resistance to outflow is low and the venous drainage rate exceeds the venous filling a negative pulse wave may be registered When the drainage rate is the same as the filling rate the venous volume will show no fluctuations although there will be a flow of blood

through the veins equal to the average rate of blood flow in the limb.

Thus the peripheral venous pulses are very much affected by the phasic changes in venous blood flow The central venous pulses are also produced in this way but in addition are directly influenced by the dynamic events of the cardiac cycle

As to the pragmatic question of the use fulness of these procedures in clinical problems this is best answered by their application to the study of subjects with disordered heart function. However this method should provide us with a method whereby the mechanical events of right heart activity may be more accurately studied An exhaustive examination of the relationship of the configuration of the waves in the "true venous pulse with events in the cardiac cycle was not the prime purpose of this study

Summary

The classic jugular phlebogram is a complex composite wave of arterial and venous origin. Mackenzie[1] suggested that if the arterial components could be removed we should have what he termed a true venous pulse wave

Methods are described whereby the true venous pulse can be recorded in directly from a central and peripheral site. The basis of the procedures is to differentially subtract the arterial volume pulse from the complex of arterial and venous volume pulsations. A comparison was made of the venous pulses and the pressure pulses recorded directly from right atrial catheterization and peripheral venipuncture.

When the "true venous pulse (TVP) is compared with the classic jugular phlebogram (JP) the most obvious difference is the reduction in size of the c wave which occurs early in systole The v h and a waves are prominently displayed on a more rapidly rising base line The negative wave X is more obvious with a rapidly descending slope from the summit of the c wave.

I wish to acknowledge the technical assistance given t arious tages of this work by R. L. W lker N de Jesús P Van Loon J T Campos nd Julio Lergier

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Relationship between the position of chest electrodes (Frank and SVEC-III systems) and the anatomic position of the heart

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In spite of the large electrocardiographic (ECG) and vectorcardiographic (VCG) literature, there is little information on variation of the relationship between the electrode position and the anatomic heart position. Only Bryant has studied the positional relation of the chest electrodes (V V) in regard to the cardiac apex by x-ray techniques and found large positional variations. For example, in a sample of men, the V position varied up to 10 cm. vertically and up to 8 cm. horizontally relative to the cardiac apex. Even the day-to-day variation of electrode placement by the same technician in the same subjects controlled by a physician was surprisingly large. This variation is included in the normal distribution for the conventional leads and may interfere to a certain extent with the recognition of abnormal changes, particularly in the anterior wall.

The variation of electrode position in reference to the heart, however, is of particular importance for corrected orthogonal lead systems, such as SVEC III, Frank, and McFee. All corrected lead systems were developed in torso model experiments, assuming a constant relationship between the heart size, heart position, and electrode position as defined by bony reference points on the chest. Investigation of variation of the relationship between recommended electrode position and heart size and heart position should be pertinent for the crucial question to what extent true electrical orthogonality can be expected in clinical application.

Subjects

One hundred and six consecutive persons scheduled for routine chest x-ray examination from Nov. 23 to Dec. 8, 1964, at the Radiology Department of the Veterans Administration Hospital in Minneapolis were investigated. Subjects with any kind of deformity of the thorax and spinal column or pathologic findings in the lungs or pleura were excluded. The subjects, 55 clinically healthy persons, 27 cardiac patients, and 24 patients with other diseases, ranged in age from 22 to 77 years.

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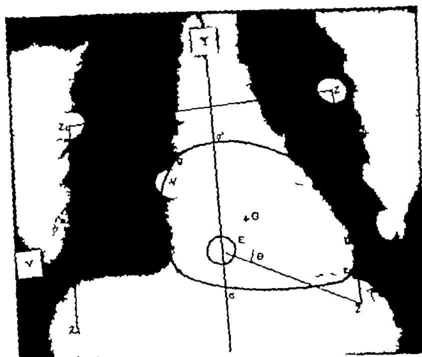


Fig. 1. A anteroposterior chest x-ray film taken with the subject in the supine position, showing the electrode positions Z, Z_2, Z_3, and Z (for the SVEC III lead system, E for the Frank lead system, and V for the conventional ECG, the outline of the heart shadow with 7 points (a, b, c, d, e, f and g), the center of gravity (G) of the heart, the X and Y reference axes, and the angle θ.

Methods

The Z positions here called Z_1, Z_2, Z and Z (Fig. 1) of the SVEC III lead system, the E electrode position of the Frank lead system (mid-sternum at the level of the fifth intercostal space) and V of the conventional ECG were chosen for the x-ray study. Although ideally the relationship between the electrode positions and the heart position should be investigated in full three-dimensional space not only with respect to the frontal plane, the analysis procedure is time consuming even with limitation to the frontal plane projection and oblique or lateral films are not very suitable for quantitative analysis.

Our study was based on analysis of the anteroposterior chest films taken with the subject in the supine position with the x-ray source above and the film behind the subject. In order to mark the electrode position clearly on the x-ray films, pennies (diameter 1.9 cm.) were attached at the 6 points (Z, Z_2, Z_3, Z_4, E, and V) on the chest wall by means of Scotch tape. The distance between the focal point of the x-ray tube and the surface of the film was adjusted to 6 feet and the x-ray beam was centered on the E point on the chest wall. The x-ray pictures were taken with respiration arrested in mid-inspiration. X-ray exposures were at 20 Ma. current, 70 to 80 Kv. with exposure of 1/4 to 1/2 second.

Fig. 1 shows the chest film of a patient in the supine position with electrode positions and heart shadow.*

Measurements on the films

The cardiothoracic ratio, the ratio obtained by dividing the transverse diameter of the heart by the transverse diameter of the thorax, was measured at the level of the intersection of the right diaphragm with the right heart shadow. This cardiothoracic ratio was expressed in percentage

*The outline of the heart shadow for all films used was drawn by Dr. Joseph Jorgens, Chief of Radiology, Veterans Administration Hospital.

On the x ray films the centers of the shadows of the pennies were marked with ink and a vertical line for Y coordinate axes, passing through the E point and midpoint between the two sternoclavicular joints was drawn. A horizontal line as an X axis, was also drawn through the E point *perpendicular to the Y axis.* Along the border of the cardiac shadow the following points were marked: point c marks the apex of heart, point e marks the intersection of the right diaphragm with the right heart shadow, and point g marks the intersection of superior vena *cava and the right atrial shadow. The intersections of the Y axis with the cardiac* border are marked by a and d, and those of the X axis with the cardiac border by b and f. The outline of the heart shadow was traced by connecting these points (a, b, c, d, f, g) with a smooth curve. We assume that, with the subject in the supine position, the anatomic heart center was at the level of one third of the sagittal diameter of the chest from the anterior chest surface and that all 7 points *were also located in a single plane passing* through the anatomic center. After the measurements of all X and Y coordinates of these 12 points (Z_1, Z_2, Z_3, Z_4, V_1, a, b, *c, d, e, f, g) on the x ray films,* parallax corrections for the image distortion due to the nonparallel roentgen rays were made *in order to determine the correct location of these points as would be seen in a parallel* x ray projection picture.

The following simple geometric expressions were used.

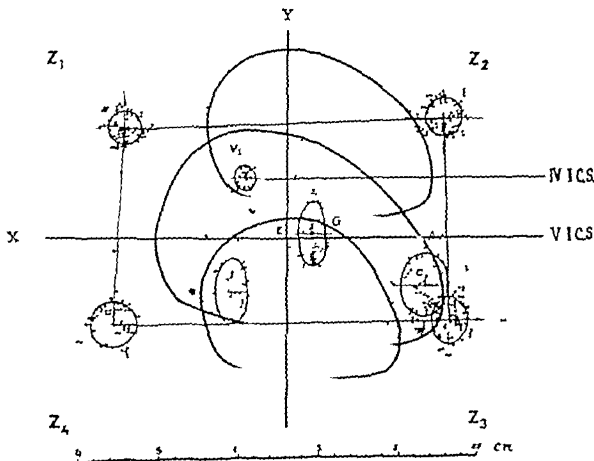


Fig. 2. Scatter diagram of 7 points (Z, Z, Z, Z, ... G) in reference to the E point in 106 cases and of V in 34 cases. The outlines of the heart shadow show the extreme high and extreme low positions found in the material, and the largest heart size (central outline).

$$Xc = Xt\left(\frac{183\text{-}D}{183}\right) \qquad Y = Yt\left(\frac{183\text{-}D}{183}\right)$$

where, Xc, Yc are the corrected X and Y coordinates
Xt, Yt are the X and Y coordinates, obtained on the teleroentgenograms
6 feet equals 183 cm
D is the measured distance between the point and the film surface.

The center of gravity of the heart shadow was determined as follows The corrected locations of the 7 points on the heart border were replotted on paper and an approximate heart figure on an orthoroentgenogram was obtained by connecting these points with a curved line. The center of gravity of this heart area was determined by a simplified estimation method i.e. two lines bisecting the heart area vertically and horizontally were drawn by eye, and the intersection of these lines was defined as the center of gravity for this area. To facilitate this procedure and improve its accuracy concentric circles and a set of X Y axes were drawn on an auxilary translucent sheet of paper This sheet was laid upon the corrected heart area pattern with the transillumination by an x ray view box, and the auxiliary sheet was adjusted to determine the estimated center The center of gravity obtained by this method coincides surprisingly well with that obtained by more traditional and more elaborate techniques. The center of gravity of the heart area was designated as point G

The scatter diagrams of X and Y coordinates of 7 points (Z_1 Z_2 Z_3, Z_4, c e G) in reference to the E point, in 106 consecutive subjects, are shown in Fig 2 The scatter of the conventional V_1 position is shown for 34 cases.

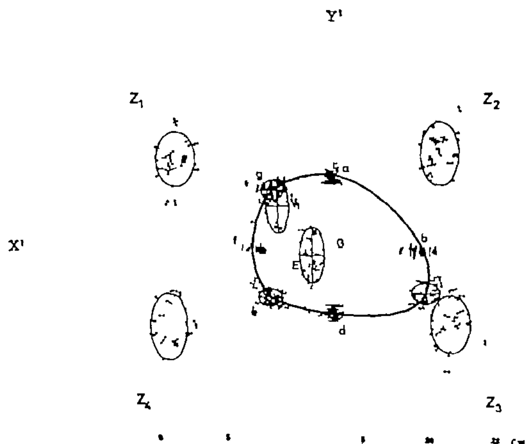


Fig 3 Two-dimensional scatter diagram of 9 points (Z Z Z4, Z c, g, E, V), nd one-dimensional scatter diagram of and d along the Y' axis and b and f along the X axis, with reference to the G point.

Next as illustrated in Fig 3 the G point on each film was taken as the reference point and new X and Y axes were drawn through G parallel to the X and Y axes drawn through E respectively The intersections of the corrected heart borders with X and Y axes are now designated as b f a d respectively and plotted as a histogram along the axis. The scatter of points a and b are only along the Y axis and that of points b and f only along the X axis, but for reason of balancing the pictures, the points in the histograms are shown slightly to the right and left for the Y axis and slightly above and below the X axis The scatter diagrams of the locations of 9 points (Z Z Z Z c e g E X) relative to the G point are also included in Fig 3 Considering that the two scatter diagrams had normal distribution in X and in Y the means and the standard deviations for the X and Y coordinates of these points were calculated Utilizing these means and the standard deviations, ellipsoids were drawn on Fig 2 and Fig 3 where axes represent the one standard deviation ranges in X and Y

Results

The variation of electrode positions in reference to the heart center is very large indeed considering that the electrodes were carefully placed according to anatomic landmarks. Table I shows the means and the standard deviations of five anatomic parameters, and X and Y coordinates of five electrode positions and two points on the outline of the heart shadow relative to E point in 106 adult subjects, except for X_1 in 34 subjects. The mean cardiothoracic ratio was 48 9 per cent, with a standard deviation of 6.9 per cent In 22 cases this ratio exceeded 50 0 per cent

On the average, Z_1 and Z were 10 43 cm to the right and Z_2 and Z were 9 92 cm to the left of the vertical line passing through E Z and Z_3 were 7 37 cm above

Table I Mean and the standard deviations of the thorax diameter the heart diameter the chest thickness the cardiothoracic ratio and of X and Y coordinates of eight points relative to the F point

	Items	*Mean (cm)*	*Standard deviation*	
			SD (cm)	*2 SD (cm)*
1	Thorax diameter (measured on the x-ray films)	29 78	2 21	4 42
2	Heart diameter	14 55	2 05	4 10
3	Chest thickness (t the F point)	22 45	2 22	4 44
4	Cardiothoracic ratio	48 9	6 9	13 8
5	G x	1 64	0 85	1 7
6	Z	−10 12	0 97	1 98
7	Z x	9 65	1 12	2 24
8	Z x	10 19	1 24	2 48
9	Z x	−10 74	1 37	2 74
10	X	−2 45	0 43	0 86
11	x	8 59	1 46	2 92
12	x	−3 17	0 96	1 92
13	G y	0 48	2 07	4 14
14	Z y	7 07	1 08	2 16
15	Z y	7 67	1 17	2 34
16	Z y	−5 27	1 44	2 88
17	Z_4 y	−5 20	1 40	2 80
18	X y	3 49	0 61	1 26
19	y	−2 99	2 00	4 00
20	y	−3 50	2 00	4 00

The small x or y means the X or Y coordinate of the point.

and Z_3 and Z were 5.23 cm below the horizontal line passing through the E point.

The average location of X_1 defined as lying at the level of the fourth intercostal space at the right sternal border was 2.45 cm to the right of and 3.49 cm above the E point.

The mean location of the G point was 1.64 cm to the left of the center line and 0.48 cm upward from the E point, closer to the fifth than to the fourth intercostal space.

The mean radial distances from the G point to Z_1, Z_2, Z_3, and Z were respectively 13.64, 10.95, 10.52, and 13.74 cm.

The quadrangles formed by Z, Z_2, Z_3, and Z had a mean length for the two sides of 20.47 cm and for the short sides, 12.54 cm. The mean of individual ratios of the short sides to the long sides was 0.61 with a standard deviation of 0.08. In 50 cases this ratio exceeded 0.61 and these individuals were considered to typify narrower thorax portions of our series.

Because the angle formed by a line connecting E and Z_3 has by definition a relationship to rib inclination, the angles formed between the line E Z_3 and X axis were measured on the films. This angle had a mean value of 27.2 degrees, with a standard deviation 7.0 degrees, with 51 cases of 106 exceeding the mean.

Generally, the standard deviations of the locations for all points were larger in the Y direction than in the X direction particularly those of the three points c, e, C on the heart shadow in Fig. 2 where two extreme positions and the largest heart shape were outlined. Among our 106 cases only 45 heart shadows were within the Z_1 Z_2-Z_3-Z quadrangle and the heart shadow in 41 cases overlapped the lower side and that in 20 cases overlapped the upper side.

The variation of anatomic heart size and location far exceeded our preconceived expectations.

The mean location of X relative to the apex point c was 11.57 cm horizontally with a standard deviation of 1.45 cm and 6.42 cm. vertically with a standard deviation of 2.18 cm. The distances between the smallest and the largest values horizontally and vertically were 6.1 and 9.5 cm respectively.

The correlation between the various electrode positions and anatomic parameters were investigated and some of them are tabulated in Table II. The lateral displacement from the midline of G locations in the horizontal direction (X axis) had a modest but significant positive correlation (0.34) with the heart diameter ($p < 0.01$), i.e. large hearts are centered farther to the left than small hearts, and also, as the heart center moves left, the cardiothoracic ratio increases ($p < 0.01$) and Z_2 and Z positions ($p < 0.01$) are more to the left. On the other hand the higher the ratio of the short side to the long side and the greater the angle θ, the lower the G point moves ($p < 0.05$). The larger the cardiothoracic ratio, the higher

Table II. Correlations between the position of G and various parameters

	Heart diameter	*Cardiothoracic ratio*	*Z*	*Z*	*Z*	*Z y*	*Angl (θ)*	*Ratio of short to long side*
G	0.34	0.34**	0.26**	0.32***				
G y		0.30***			0.23**	0.26***	−0.22**	−0.21

*X correlation.
**Significant, < .05
***Significant, < 0.01

Table III The means and the standard deviations of X and Y coordinates of 13 points relative to the G point in 106 cases except that of V₁ which was measured in 34 cases

Z (cm)	*Z (cm)*	*Z (cm)*
X = −11 69 ± 1 21	X = 8 02 ± 1 44	X = 8 61 ± 1 50
Y = 6 68 ± 2 11	Y = 7 19 ± 2 29	Y = −3 66 ± 2 15
Z (cm)	*a (cm)*	*b (cm)*
X = −12 20 ± 1 39	X = 0	X = 6 54 ± 1 00
Y = −5 86 ± 2 53	Y = 5 58 ± 0 54	Y = 0
c (cm)	*d (cm)*	*e (cm)*
X = 6 89 ± 1 00	X = 0	X = −4 84 ± 0 87
Y = −3 20 ± 0 89	Y = −4 85 ± 0 54	Y = −3 64 ± 0 66
f (cm)	*g (cm)*	*E (cm)*
X = −6 08 ± 0 88	X = 4 53 ± 0 93	X = −1 64 ± 0 84
Y = 0	Y = 4 40 ± 0 63	Y = −0 48 ± 2 06
V (cm)		
X = −4 06 ± 1 03		
Y = 3 14 ± 2 07		

becomes the location of C ($p < 0.01$)

Fig 3 shows large variation of the electrode positions relative to G points and the average outline of the heart shadow (a b c d e f and g) The means and standard deviations are shown in Table III and can be seen graphically in Fig 3 The variation of electrode position is greater vertically than horizontally whereas the heart border (c e g) varies more horizontally than vertically relative to C

Discussion

The investigation reveals an unexpectedly large interindividual variability of the electrode positions in relation to anatomic reference points on the chest (Frank s E electrode position) Size circumference and location of the heart shadow were also more variable than expected Although some significant correlation to anatomic features of the thorax are found the correlations are far too low to permit simple development of correction factors. It should be noted that the placement of the electrodes in all cases was done with great care by one experienced operator These values might therefore be considered to be the minimum variation to be expected in the clinical application of corrected orthogonal VCG levels Additional variation of electrode placement should be expected when other or less experienced investigators mark the electrode positions The sample is reasonably representative of patient material in a general hospital This large variability should be taken into account in the design of corrected lead systems and may limit the extent to which electrical orthogonality can actually be achieved in routine clinical vectorcardiography

The variability of electrode placement per se also affects the uncorrected lead systems. Where these leads are electrode points remote from the heart, as in some of the cube and tetrahedral arrangements the actual electrode positions probably become less critical but the lead may indeed become very sensitive to heart positions since this is variability against which at least some of the corrected lead system are protected Simple leads, such as the classic precordial leads are exaggeratedly sensitive to electrode position relative to the heart and chest

The large uncontrolled and mainly uncontrollable effect of electrode position is probably an important factor in the wide range of the normal distribution in magnitude and orientation of instantaneous spatial vectors for instance in the result of Draper and associates.

In a separate study by Horibe Okamoto

Simonson and Schmitt,[7] significant changes in orientation and magnitude of spatial vectors recorded with four different lead systems were obtained on displacement of electrode positions by 2 cm. which is below 2 standard deviations of anatomic variation for most parameters, as shown in Table II Variation of electrode position in a given subject is reasonably comparable to interindividual anatomic variation in so far as electrical orthogonality is concerned.

Summary

The relationship between the four chest electrode positions of the SVEC III Z lead the conventional V_1 lead and the heart position and size was studied in x-ray films taken in the anteroposterior projection, with the subject in mid-inspiration and in the supine position. The sample of 106 consecutive patients consisted of 55 clinically healthy persons, 27 cardiac patients, and 24 patients with other disease. The position of the electrode marked by pennies on the chest wall with respect to the location of the E electrode of Frank lead system and with respect to the center of gravity of the heart shadow and other identifiable points on the heart shadow was measured in X and Y coordinates, and corrected for parallax. The distribution and variation are expressed in vertical (Y-axis) and horizontal (X-axis) standard deviations and are shown with ellipsoid distribution diagrams. The variability of the electrode positions both in regard to G and to E was very large more so in the vertical than in the horizontal direction. There was some correlation of chest dimension heart size position and configuration with electrode positions, but the correlations were too low for reliable prediction In view of the large variability of electrode position the degree of orthogonalization that can be achieved with conventional corrected leads in clinical routine vectorcardiography becomes questionable and the task of devising individual anatomically based correction factors becomes more difficult.

We wish to express our thanks to Dr Joseph Jorgens Professor of Radiology University of Minnesota, and Chief of the Department of Radiology Veterans Administration Hospital, Minneapolis, Minn., for his advice throughout this study

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The intracardiac electrocardiogram of human atrioventricular conducting tissue

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The electrical activity of the conducting system of the heart has been directly recorded in experimental animals both by intracellular ultramicroelectrodes and by small surface or extracellular electrodes placed on or near conducting tissue. It has also been directly recorded from the human bundle of His in attempts to avoid the production of heart block during open heart surgery.[1-4]

Giraud and his colleagues[5] (1960) have recorded potentials from the bundle of His with an electrode catheter during cardiac catheterization in a patient with the trilogy of Fallot. They also found deflections ascribed to atrioventricular (A-V) conducting tissue in 20 per cent of their cases of atrial septal defect, emphasizing that repeated and prolonged exploration of the appropriate region of the atrial septum was necessary. Those workers describe *the A-V nodal electrogram* as one of small voltage (0.1 to 0.25 millivolt), more often positive than negative, and slowly inscribed over 30 to 40 milliseconds. It begins about 100 to 120 milliseconds after the onset of atrial depolarization and about 10 to 30 milliseconds after its completion (i.e., after the end of P), but is of course proportionately later in patients with long P waves or prolonged P-R intervals. *The electrogram from the bundle of His* occurs a little later, about 130 milliseconds after the onset of P, and is of shorter duration (20 milliseconds). It has a diphasic morphology with a characteristically rapid intrinsic deflection. During the course of careful exploration with electrode catheters of more than 700 hearts, including 100 with atrial septal defects, we have only once seen convincing evidence of the electrical activity of the conducting tissue.

Observations

The patient was a 14-year-old girl with Ebstein's anomaly of the tricuspid valve. Although she had no symptoms, and her heart was not enlarged, there were typical abnormalities on auscultation and in the electrocardiogram. At cardiac catheterization with an electrode-tipped Cournand catheter a chamber was demonstrated in which an atrial pressure pulse was accompanied by a ventricular intracardiac electrocardiogram (Fig. 1), findings characteristic of the *atrialized* portion of the right ventricle formed by the downward displacement of the tricuspid valve in Ebstein's anomaly.

A small sharp deflection between the end of the P wave and the onset of the QRS complex in the intracardiac electrocardiogram was consistently present in

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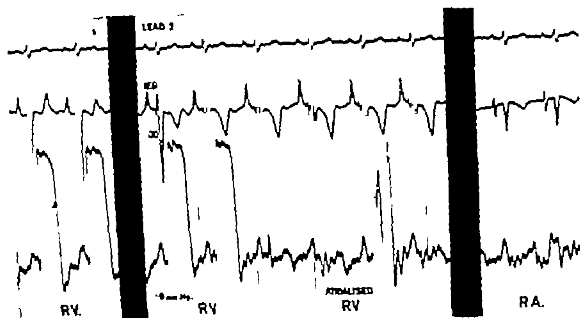


Fig. 1 The type of record sometimes seen in Ebstein's anomaly when displacement of the tricuspid valve causes atrialization of the proximal part of the inflow tract of the right ventricle. Records made in this chamber with an electrode-tipped Cournand catheter may show a ventricular intracardiac electrocardiogram and an atrial pressure pulse. In this case, a small extra deflection—thought to originate in the bundle of His or its right branch—appeared between the end of P wave and the onset of the QRS complex, and was persistently present in recordings made near the tricuspid valve as evidenced by "valve slap" artefact on the pressure pulse tracing.

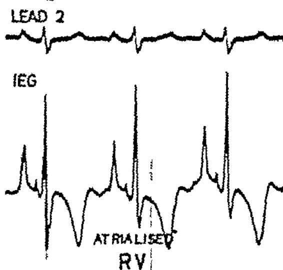
numerous withdrawal tracings recorded as the electrode at the tip of the catheter passed through this atrialized chamber from the right ventricle proper into the right atrium (Fig. 2). It was diphasic (+ −), had a duration of about 20 milliseconds, an amplitude of 0.2 to 0.3 millivolt, and occurred 140 to 160 milliseconds after the onset of P, the P-R interval being 200 milliseconds.

This deflection appeared simultaneously with the last one or two ventricular pressure pulses during slow withdrawal from the distal part of the right ventricle, persisted as the tip of the catheter was pulled back through its atrialized portion, and disappeared when the true right atrium was reached. It was most obvious on tracings recorded near the tricuspid valve cusps, as evidenced by "valve slap" artefacts on the pressure pulse tracings.

Discussion

The intracellular ultramicroelectrode has demonstrated that the sinus node, atrioventricular (A-V) node, bundle of His, and Purkinje fibers have different transmembrane action potentials characteristic for each location and presumably reflecting different physiologic properties, particularly the rate of conduction.[8-11] Propagation of the cardiac impulse through every part of the conducting system from the sinus node to the Purkinje network and ventricular muscle can be analyzed by small unipolar or bipolar surface electrodes placed either in contact with these tissues or, in the case of the A-V conducting system, within 2 mm. of it.[12-14]

In the dog, epicardial surface electrodes demonstrate activity of the sinus node in a very small area near the junction of the superior vena cava and right atrium. A unipolar lead shows an entirely negative P wave with several notches on the descending limb; a bipolar lead, its points separated by a distance of 0.2 mm. or less, shows a multiphasic complex of low voltage preceding the start of the P wave by about 25 milliseconds.[12-4] Puech and his colleagues[15] have carefully mapped out the course of activation of the dog's atria



F g 2 A large en of the l tracardiac lectro rdiog m how that the morphology nd time relationsh ps of he extra deflection satisfy the criteria proposed by experimental workers for excit ion of A V onducting tissue (small l nes = 40 m lliseconds

using epic rdial electrodes and Watson[22] has explored the endocardi l aspects of the atria with an electrode catheter during the n estigation of patients with atrial septal defects and other congenital cardiac malform tions.

Th principal site of delay in atrioventricular conduction is near the junction of the atrium and A V node where the rate of conduction is about 0 02 to 0 05 meter per second (M sec) as comp red with 0 12 M sec for the A V node 0 8 to 1 0 M sec for atrial muscle and 2 to 4 M sec for the bundle of His. [u 23] The spread of excitation through the A V conducting system can be timed l y relatin, the elec trogram to the standard scalar electrocardiogram A V nodal excitation occurs during the P R interval before the point about two third of the way between the end of the l wave and the beginning of the QRS complex at which the electrogram of the bundle of His is recorded [4] The A V nodal electrogram is of small amplitude and duration (25 to 40 milli seconds) in the dog As would be expected its morphology is negative at the atrial end dipha ic (+ −) in the middle and positive as it reaches the bundle of His. [23]

The electrogram of the bundle of His is of short duration (20 milliseconds) and has a diphasic (+ −) morphology with a sharp intrinsic deflection The electrograms of the right and left branches are of rather smaller amplitude and duration than that of the parent bundle they are diphasic and show rapid inscription of the intrinsic deflections.[23] To record the electrical activity of the Purkinje network it is necessary to insert fine electrodes into the ventricular endocardium where a small and usually biphasic impulse is recorded immediately before the ven tricular complex.[23]

Much of our present knowledge is thus deri ed from animal experimentation and only recently has it been possible to map out accurately the excitation patterns of the human heart.[24] We have never before recorded an electrical potential resembling the one that we now report. It does not look like any known artefact Its shape and location are those of the electrogram of the bundle of His, although it is not possible to say whether it was deri ed from the main bundle or its right branch or even from both because it was recorded during *withdrawal* of the electrode through the proximal ventricular chamber or atrial ized ventricle

The A V node is situated on the atrial side of the base of the tricuspid valve near the junction of its posterior and septal leaflets. The A V bundle which is sometimes composed of several fascicles of fibers passes through a thickened part of the annulus fibrosus to reach the posterior and inferior margins of the membranous septum and thence takes one of several routes along the upper part of the muscular septum between layers of the mem branous septum or under the right or left ventricular endocardium before dividing into its main branches. The right bundle branch usually arises beneath the mem branous septum and descends to the base of the papillary muscle of the conus and is sometimes buried in ventricular muscle for part of its route The precise anatomy of the A V conduction system is a difficult and controversial sul ject because of the technical difficulties of its dissection and the wide variation in its distribution [n 11] Nevertheless when anatomists seek to



Fig 3 Dissection of the right heart of an inf t who died with Ebstein anomaly illustrates the pathologic anatomy of the tricuspid valve cusps. The trium has been widely opened and as one looks down into the ca ity of the right entricle it is clear that in such a case the A V conducting tissue is unduly accessible to an exploring electrode. *a*, Foramen ovale. *b* Tiny septal cusp Vestigial posterior cusp. *d*, Bare endocardium. Right atrial appendage *f* Atrioventricular ring *g* Large sail-like anterior cusp.

demonstrate the A V conducting tissue they usually first remove the posterior and septal leaflets of the tricuspid valve so as to expose the area in which the conducting tissue lies.

In Ebstein's anomaly the septal leaflet of the tricuspid valve is often absent or vestigial and the posterior leaflet is deformed and displaced distally arising from the ventricular endocardium instead of from the annulus fibrosus (Fig 3) The bundle of His and its right branch are therefore likely to be more accessible to an exploring electrode than they are in any other condition. Despite this, we have been unable to record similar deflections in 7 other patients with this lesion and can only suppose that this is because of the wide variation that occurs in the nature of such valves.

Giraud and his colleagues[4] reported that they found A V nodal electrograms in patients with either ostium primum or ostium secundum type of atrial septal defects. These were recorded when the intracardiac electrode lay near the A V conducting tissue either low in the right atrium or in a low atrial septal defect or in the coronary sinus and were more easily recognized during supraventricular arrhythmia.

We have not recorded such potentials during the careful catheterization of 100 cases of atrial septal defect, and cannot explain this discrepancy between our experience and that of the Montpellier group.

Summary

Deflections that satisfy the criteria proposed by experimental workers for excitation of the bundle of His or its right branch have been recorded on intracardiac electrocardiograms during cardiac catheterization in a patient with Ebstein's anomaly of the tricuspid valve.

We have never before seen such potentials despite careful exploration with electrode catheters during the investigation of more than 700 hearts with congenital or acquired lesions and suppose that the pathologic anatomy of the valve cusps in Ebstein's anomaly may make A V conducting tissue unusually accessible to the exploring electrode.

W are gratef l to Dr K. Rhaney and Mr R. S Fox for the photograph i Fig 3

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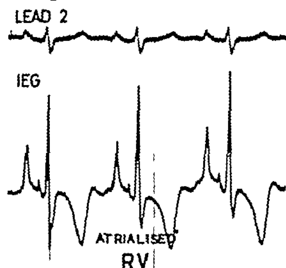


Fig 2 An enlargement of the intracardiac electrocardiogram to show that the morphology and time relationships of the extra deflection satisfy the criteria proposed by experimental workers for excitation of A V conducting tissue (small lines = 40 milliseconds)

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We are grateful to Dr. K. Rimney and Mr. R. S. Fox for the photograph in Fig. 3.

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Effects of acute digitalization on cardiovascular dynamics in experimental, surgically induced heart block

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Complete heart block remains a serious complication of open heart surgery In early reports, the incidence of third degree heart block was as high as 30 per cent after repair of interventricular septal defects. With improved understanding of the anatomy of the conduction system the frequency of surgically induced heart block has gradually declined. In 1962 Gerbode and Keen found that the over all risk of complete heart block in patients undergoing ventricular septal defect repair was 10 per cent. An identical incidence was reported by Lillehei and his colleagues[3] in a group of patients with surgical correction of ventricular septal defect, tetralogy of Fallot and atrioventricularis communis, and the same incidence occurred in total correction of tetralogy at the Johns Hopkins Hospital. Only 16 of 689 patients had complete heart block after repair of ventricular septal defect, in a series reported by McGoon Ongley and Kirklin[4] in 1964 Complete heart block may also complicate prosthetic valve replacement and cardiac catheterization. [7] Normal conduction returns, over a period of several weeks, in about two thirds to three fourths of patients but permanent heart block unless successfully treated, carries with it a very poor prognosis.

The treatment of heart block complicating open-heart surgery has included transvenous and implanted cardiac pacemakers[8] infusions of isoproterenol, and in some cases, watchful waiting since the heart block may be transient. The role of digitalis in the treatment of heart block is controversial[10-11] yet cardiac dynamics are frequently impaired in the immediate postoperative period as a result of the intrinsic heart disease cardiopulmonary bypass, and cardiotomy The purpose of this study was to evaluate the effects of acute digitalization on cardiovascular dynamics in experimental, surgically induced heart block.

Methods

Twelve dogs (13 to 16 kilograms) were anesthetized with intravenous sodium pentobarbital (25 mg per kilogram) and venti

With the technical assistance of Nicholas J. Vanle.
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lated mechanically through a cuffed endotracheal tube with 100 per cent oxygen. The heart was exposed through a right lateral thoracotomy. With temporary venous inflow occlusion and a right atriotomy approach, complete (third-degree) heart block was produced in 10 of the 12 dogs by placing a ligature through the atrioventricular nodal area.[13] In the other 2 dogs ventricular fibrillation developed and the experiment was terminated.

In each dog the femoral artery and femoral vein were cannulated. Catheters were advanced retrograde to the left ventricle and the right atrium, respectively, through left carotid artery and right jugular vein cutdowns. Pressures were recorded from the left ventricle and the femoral artery by means of Statham 23Db transducers connected to a multichannel Sanborn 350 recorder. With an RC filter having a time constant of 5×10^{-3} seconds in the recording amplifier of the left ventricular channel, the left ventricular catheter transducer system had a flat frequency response to 16 c.p.s. and a cutoff of 20 db per decade at 20 c.p.s. High-sensitivity tracings of left ventricular pressure were taken in order to measure left ventricular end-diastolic pressure. The first derivative of left ventricular pressure was recorded through the use of an analog RC differentiating circuit with a time constant of 44×10^{-4} seconds. Lead II of the electrocardiogram was also recorded. Paired cardiac outputs were obtained by the indicator-dilution technique by means of injections of indocyanine green into the right atrium and sampling from the femoral artery.

With a sine wave Medicon flowmeter, a flow probe was placed around the ascending aorta, and instantaneous aortic flow was recorded on the multichannel Sanborn. Calibrations were made by comparing the mean aortic flow against simultaneous cardiac outputs obtained by the indicator-dilution technique. Instantaneous stroke volume was electronically computed from the aortic flow recording through the use of an integrator circuit which was reset after each heartbeat by the electrocardiographic QRS complex.[13] Stroke volume was also calculated from the indicator-dilution cardiac outputs.

After heart block was surgically produced, each experimental animal was allowed to stabilize for about 30 minutes, and base-line measurements of pressure and flow were obtained. Acetylstrophanthidin (0.03 mg. per kilogram) was then infused intravenously over 5 minutes, and repeat doses of acetylstrophanthidin were given at 20-minute intervals until digitalis toxicity developed as manifested by ventricular or nodal tachycardia. Measurements of pressure and flow were recorded at intervals of 5, 10, and 20 minutes after the first and subsequent infusions of acetylstrophanthidin.

Statistical analyses. The data were evaluated by applying Student's "t" test with use of paired-sample analyses rather than the difference between control and experimental means.

Results

The pertinent hemodynamic data recorded before and at 20 minutes after the first dose of acetylstrophanthidin are presented in Table I. After acetylstrophanthidin there was a significant increase ($p < 0.05$) in mean systemic arterial pressure, peripheral vascular resistance, the rate of rise in left ventricular pressure, left ventricular minute and stroke work, and peak aortic flow. An average decline of 26 per cent in left ventricular end-diastolic pressure was not significant ($p < 0.10$). Cardiac output and heart rate as

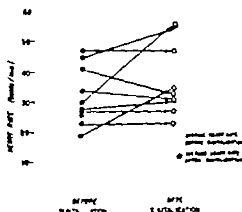


Fig. 1. The effect of acute digitalization on heart rate in each of 10 animals with surgically induced heart block.

Table I Hemodynamic data

Dog	Mean systemic pressure (mm. Hg)	Cardiac output (L./min.)	Peripheral vascular resistance (× 10³ dynes sec. cm.⁻⁵)	dp/dt* (% base line)	Lt. vent. work (Kg. M./min.)	Stroke work (Gm. M./beat)	Heart rate (beats/min.)	Left ventricular end-diastolic pressure (mm. Hg)	Peak aortic flow (% base line)
1. Control	90	1.70	4.25	100	2.04	43.4	34	6	100
Dig	80	1.63	4.85	175	1.70	36.1	31	6	134
2. Control	45	0.92	3.91	100	0.30	15.8	28	12	100
Dig	70	1.23	4.60	142	1.10	31.4	31	7	119
3. Control	115	2.10	4.40	100	3.10	68.9	30	12	100
Dig	130	2.26	4.60	162	4.00	72.7	56	5	127
4. Control	35	2.18	1.30	100	0.90	21.9	26	6	100
Dig	40	1.85	1.74	113	0.90	27.7	26	6	120
5. Control	40	0.94	3.40	100	0.31	10.3	37	17	100
Dig	70	1.14	4.90	105	0.99	17.7	27	9	128
6. Control	38	0.60	5.05	100	0.22	8.5	23	12	100
Dig	45	0.67	5.38	137	0.30	11.8	23	13	108
7. Control	43	0.68	3.05	100	0.37	13.7	47	4	100
Dig	55	0.67	6.55	188	0.48	17.7	47	4	100
8. Control	44	1.23	2.64	100	0.76	33.0	19	4	100
Dig	60	1.70	2.80	125	1.34	38.2	35	5	90
9. Control	43	1.23	2.92	100	0.61	17.9	45	10	100
Dig	50	1.50	2.66	144	0.94	30.3	35	6	116
10. Control	60	0.92	5.30	100	0.65	23.2	41	10	100
Dig	105	1.23	6.70	138	1.74	56.1	33	8	104
Average									
Control	55	1.26	3.82	100	0.93	25.7	32	9.3	100
Digitalis	70	1.39	4.48	143	1.35	35.9	36	6.9	115
% Change	+27	+10	+17	+43	+45	+39	+12	−26	+15
p Value	<0.05	<0.?0	<0.05	<0.01	<0.05	<0.05	<0.3	<0.10	<0.05

*dp/dt Rate of rise in left ventricular pressure
Dig Digitalization

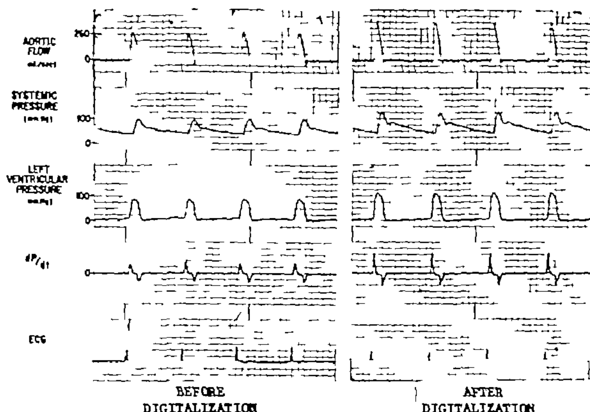


Fig. 2. Pressure flow and electrocardiographic recordings before and after digitalization in an animal with acute surgically induced heart block. Peak aortic flow, systemic pressure, and the rate of rise in left ventricular pressure are increased without change in heart rate. Paper speed is 25 mm. per second.

well as stroke volume were not significantly changed after acetylstrophanthidin. The effect of acute digitalization on the heart rate in each of the 10 experimental animals is presented in Fig. 1.

The recordings of pressure and flow before and after digitalization in one of the experimental animals are illustrated in Fig. 2. In of the 10 experiments, there was increased stroke work at the same or at a reduced left ventricular end-diastolic pressure after acute digitalization (Fig. 3). The over-all trend was a shift of the left ventricular function curve to the left and upward in the direction of a positive inotropic effect.

Acetylstrophanthidin was given in successive doses of 0.03 mg. per kilogram at intervals of 20 minutes until the development of toxicity was manifest by ventricular or nodal tachycardia. After the first dose of acetylstrophanthidin there was no change in the electrocardiographic QRS complex in any of the animals studied and ventricular or nodal tachycardia was not observed. Toxic ventricular or nodal rhythms developed after the second dose of acetylstrophanthidin in 3 dogs, after the third dose in 6 dogs, and after the fourth dose in 1 dog.

Discussion

The positive inotropic characteristics of digitalis in normal and failing hearts have been well defined.[18] In addition, digitalis has a vagal depressant effect on the sinus and atrioventricular nodes as well as on the bundle of His.[7] Since these parasympathomimetic actions of digitalis may further reduce the ventricular rate in heart block,[19] there has been a reluctance to administer digitalis in the presence of th conduction disturbance. In man with chronic heart block and congestive heart failure, Bellet found that the administration of digitalis did not improve cardiac

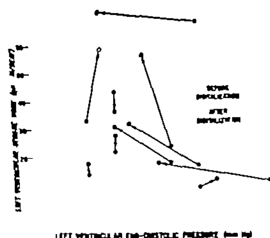


Fig. 3. A plot of the relationship between left ventricular stroke work and ventricular end-diastolic pressure before and after digitalization in 10 animals with acute heart block. See text for details.

output and stroke volume and heart rate remained constant at a fixed low rate. In the dog with surgical heart block, Willman and his associates[20] observed that the inotropic effect of digitalis in "nontoxic" doses was negated by a reduction in heart rate. A marked increase in cardiac output was noted when a toxic nodal tachycardia developed. At variance with these findings were those of Schwartz and Schwartz, who observed an inotropic effect of digitalis without a change in rate in patients with complete heart block. More recently, Benchimol and associates[21] demonstrated a marked improvement in cardiac dynamics after digitalization in patients with heart block who were being artificially paced at a fixed ventricular rate. There was an increase in cardiac output and stroke volume and a decrease in systolic ejection time and the duration of mechanical systole.

In the present study of complete heart block, acute digitalization significantly improved cardiovascular dynamics without altering the heart rate. Peripheral vascular resistance was increased after the administration of acetylstrophanthidin and blood pressure rose accordingly without significant change in cardiac output. The increase in peak aortic flow without alteration in stroke volume is consistent with a shortening of mechanical systole as found by Benchimol and associates.[21] In addition the positive inotropic effect of acetylstrophanthidin on the myocardium was demonstrated by an augmented rate of rise in left ventricular pressure[22] and an increased stroke work at the same or at reduced ventricular end-diastolic pressure in 7 of the 10 animals.[23] The dose of acetylstrophanthidin employed was well within the therapeutic range and the aforementioned hemodynamic changes were noted after the initial dose of acetylstrophanthidin (0.03 mg. per kilogram). Digitalis toxicity as manifested by a nodal or ventricular tachycardia did not develop until at least twice the initial dose of acetylstrophanthidin.

The results observed in the present study indicate that digitalis therapy should be safe and beneficial in patients with surgically induced complete heart block. Cardiac dynamics were improved in otherwise normal dogs that had no underlying myocardial disease. One might expect even greater improvement with the administration of digitalis to patients with postoperative heart block, in view of the cardiodepressant effects of cardiotomy and cardiopulmonary bypass.

Summary

In 10 dogs with surgically induced heart block, acute digitalization significantly improved over-all cardiovascular dynamics without altering the heart rate. Peripheral vascular resistance, mean systemic pressure, and left ventricular pressure were significantly increased after the administration of acetylstrophanthidin. There was no significant change in cardiac output or left ventricular end-diastolic pressure. These findings indicate a beneficial effect of digitalization in acute surgically induced heart block.

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Pacemaker attachment to the cardiac conduction system in experimental heart block

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Heart block was first treated clinically by Weirich and others in 1957[1,2] with an external pacemaker for temporary control of surgically induced heart block. Hunter and associates, in 1959 reported the use of a bipolar electrode. Chardack and co-workers,[4] in 1960 reported on the use of an entirely internal pacemaker with small cadmium mercury batteries as a power source. Since that time over 4 000 units have been implanted Stimulated by our interest in the conduction system we questioned whether it might be advantageous to attach at least one of the electrodes to the conduction bundle.

Material and methods

Using the technique reported earlier in dogs of cutting and then cauterizing the conduction bundle in the right atrium under conditions of inflow occlusion we induced complete heart block in 5 adult mongrel dogs each weighing from 30 to 40 pounds. To induce anesthesia a 2½ per cent solution of sodium Pentothal was injected intravenously in doses sufficient to induce a level of surgical anesthesia. Assisted respiration was maintained with a mechanical respirator A right lateral thoracotomy was performed through the fifth intercostal space During the same exposure as that used to induce complete heart block in each of the dogs, an electrode (Medtronic) was attached to the conduction bundle by means of a stainless steel wire implanted just distal to the cut conduction bundle and brought out through the right atrial wall and then through the thoracic wall. In addition electrodes were attached in the usual manner to the left ventricle and brought out through the thoracic wall After the thoracic wound was closed with the animal still anesthetized but breathing unassisted studies of cardiac output were made under conditions of (1) no pacing (2) pacing through the two left ventricular electrodes, and (3) pacing through the system which included the electrode placed in the conduction system In this procedure the second electrode was one of the two that had been implanted in the left ventricular wall Pacing was done at the rate of 90 beats per minute, through the use of an external pacemaker

Determinations of cardiac output were

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made with the use of Cardio-Green dye and a densitometer.[4] The dye was injected into the anesthetized animal through a vein in the right foreleg and blood was withdrawn from the left femoral artery. Values for cardiac output were converted to cardiac indices (cardiac output in liters per minute per square meter). For each condition in each dog, two and sometimes three determinations were made and averaged for the values given in Table I. Reproducibility of the determinations was within 5 per cent. A total of 50 studies for cardiac output was made on the 5 animals.

Results

There w s i n istent incr ise in cardiac output when the nduction bundle w is stimulated (T ble I) as compared to the result when timulation was through the two l ft v ntricular electrodes. There appeared t be nc differences in the elec trocardiogram in the three standard leads between these two meth ds of pacing. The improvement with stimulation of the con duction bun ll is compared to conven tional left ventricular stimulation varied from 15 t 83 per cent with the cardiac index aver iging about 20 per cent greater or 0 3 l min M

Comment

The experiments lescribed indicate that under conditions of recently induced complete heart block a greater cardiac output is obtained when pacing is done by way of one electrode imbedded in the distal segment of the bundle of His than when each electrode is imbedded in the left ventricular wall. This raises the question of whether the method used experimentally could have practical application in the treatment of complete heart block.

To this end preliminary studies have been made in 3 dogs with complete heart block induced 4 8 and 10 months previously. In the first 2 animals one electrode was connected to the conduction system as herein described and the other electrode was implanted in the left ventricular wall. Each electrode was connected to a permanent pacemaker (Medtronic) which was implanted subcutaneously. In the third dog the electrodes were joined to in implanted pacemaker (Medtronic) with both electrodes implanted on the left ventricular wall. The cardiac index in the 2 dogs with the conduction bundle electrode averaged 2 8 l min M² in the dog with usual ventricular electrodes it averaged 2 2 l min M² or about 27 per cent better with the conduction bundle electrode.

Summary

In 5 dogs with recently induced complete heart block two methods of pacing were compared with respect to index of cardiac

Table I. Cardiac outputs (a) in experimental complete heart block (b) with pacing through electrodes attached in usual manner to the wall of the left ventricle and (c) with pacing utili ing a conduction bundle elect ode

Date	Dog number	Heart block: Cardiac output (L/min)	Heart block: Cardiac index (L/min/M²)	Both pacing two ventricular electrodes: C.O. (L/min)	C.I. (L/min/M²)	Per cent improvement	Both pacing one ventricular and one conduction bundle electrode: C.O. (L/min)	C.I. (L/min/M²)	Per cent improvement
Nov 3, 1965	1	1 9	1 3	1 7	1 1	—15	2 2	1 8	15
Oct. 28, 1965	2	1 0	0 7	1 2	0 8	14	1 2	0 8	14
Nov 10, 1965	3	1 6	1 2	1	1 5	25	2 6	1 9	50
Nov 12, 1965	4	1 9	1 4	5	1 9	35	2 7	2 0	42
Nov 22, 1965	6	0 9	0 6	1 1	0 9	50	1 3	1 1	83
Average		1 4	1 0	1 7	1 2	21 9	2 0	1 5	40 9

C.O. Cardiac output; C.I. Cardiac index.

output In one condition the two electrodes were implanted in the left ventricular wall In the other condition one electrode was implanted in the left ventricular wall and the other was implanted in the *conduction tissue* distal to the level of the section This made for induction of complete heart block.

The cardiac index was greater under the conditions of stimulating the conduction tissue directly than with the other method

Further studies should be made in order to determine whether the method of stimulating the conduction tissue is of value in chronic complete heart block.

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Discrimination of the quantitative ultralow frequency ballistocardiogram in coronary heart disease

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Waveform abnormality of ballistocardiograms has long been associated with manifest or suspected coronary heart disease (CHD). Characterization of waveforms as normal, borderline, or abnormal, however, is highly subjective and poorly suited to analysis by mathematical methods. In this investigation, objective measurements of ultralow frequency (ULF) acceleration ballistocardiograms (BCG) have been made in order to explore their usefulness in the discrimination of coronary heart disease. Both resting and postexercise recordings were studied.

Using programs written for the IBM 7094 computer, we have employed the statistical methods of regression, correlation, and discriminant analysis. The effectiveness of these procedures is enhanced by the use of "continuous variables," such as amplitude and slope measurements, in comparison to "discrete variables," such as normal-borderline-abnormal. Several of the wave measurements individually, as well as discriminant analyses using combinations of them, show significant differences between normal and cardiac groups and a meaningful scaling of individuals in the test population. Comparison of these results is made with earlier studies in which other BCG criteria were used for classification.

Materials and methods

Two groups of men were studied: normal subjects and cardiac patients. The first group was composed of 20 persons whose blood pressure, heart size by x-ray film, resting 12 lead electrocardiogram, and cardiovascular history were normal by commonly applied standards. In the opinion of the examining physician, no person in this group had ever experienced chest pain either typical or atypical of that of ischemic or coronary heart disease. There were 24 persons in the cardiac group. As with the normal subjects, these patients all had blood pressures of less than 140/90 mm. Hg except for one whose systolic pressure was 150 mm. Hg. None of them was judged to have cardiomegaly or heart failure. All were considered to have coronary heart disease either by documentation of an old myocardial infarction or by classic angina pectoris as judged by one or more of the

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contributing and reviewing physicians. The patients and control subjects were age-matched by decade with mean ages of 46 and 49 years, respectively. Average weights for the two groups were 159 pounds for patients and 163 pounds for normal subjects.

An advanced type of ultralow-frequency ballistocardiograph was used in the study. This instrument was described in detail in a previous report. In this investigation the lateral motion feature of the machine was eliminated because lateral records were not taken. Although the equipment possessed the desirable qualities of long period and relatively light (16 pounds) platform, several minutes were usually required for adjustment after the patient lay down on it. This delay was a handicap in observing the patient's postexercise response and will be discussed later. The electrical circuitry was arranged so that a calibration signal representing acceleration of known amplitude could be inserted into the record at any time during the test.

Concurrently with the head-foot ballistocardiogram, a timing electrocardiogram (Lead II), phonocardiogram, and pneumogram were recorded. These four records were displayed on a multichannel direct-writing oscillograph of adequate frequency response, either a Schwarzer Physioscript or Century Electrograph. Fig. 1 is a section from a typical recording. During exercise testing of the cardiac patients, there was continuous monitoring by a set of special ECG chest leads. Postexercise monitoring by the same lead system was continued while the ballistocardiogram was being recorded using a second direct-writing recorder.

The patients were not fasted. They were rested for approximately 10 minutes prior to study, during which electrode connections were made and instructions given. An initial resting record, including one or more respiratory cycles, was then taken.

Exercise by the subjects took any of three different forms: stair climbing, pedaling a bicycle ergometer, or performing the double two-step test according to Master's criteria. Because in-exercise ECG monitor

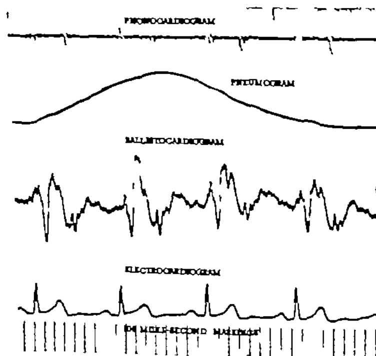


Fig. 1. Section from the recording of a typical normal subject. The electrocardiogram is used as a timing reference only.

Table I The fourteen BCG variables studied in basal and exer ise onditions

Amplitudes	G-H	G-I	G-J
Slopes	G-H	H I	I J
W pe	CH HI IJ—simple dur jog not h H tip t pe—simple or split		
Times	R H and R I seconds		
	R H and R I per ent of heart period		

ing was not con idered to be necessary on some of the younger n rmal subjects they alone were subjected t st ir climbing End points of the tests were set by completion of the prescribed exercise in the case of the Mast r test and tair climbing by pain ex essive fatigue or an ischemic ECG response The effect f this nonuniformity of exercise i believed to be a larger variability of result than would otherwise be present and not to cause any significant bias in the normal versus cardiac comparisons

Fourteen variables (Table I) were measured in both resting an l postexercise states. These fell into four main c tegories ampli tudes slopes times and wave types. Fig 2 is a schematic ballistocardiogram on which the measured quantities are identified Ancillary information such as height weight age, and respiratory phase in which a particular heartbeat occurred were also coded and punched on the data cards. Breathing was phasic throughout A six part respiratory phase classification was used early mid and late inspiration and expiration Analyses were made separately for each respiratory phase as well as for the data averaged over the complete breathing cycle. In order to have some control over the objectivity of the measurements, simple criteria in regard to the sites of measurement of the waves were applied The measurements were always carried out over one or more complete respiratory cycles in an attempt to eliminate bias from this source All records were screened for technical quality by an experienced observer and measured by disinterested operators. No attempt to employ blind technique was made but it was thought that the criteria for measurement tended to minimize if not eliminate bias.

Results

All 14 of the measured variables, both basal and postexercise were tested for

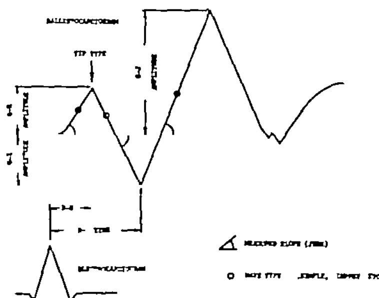


Fig Schematic representat on f BCG o showing the quantities me sured or tegorized

Table II *The three variables used in a discriminant analysis*

Variable	*Normal*		*Cardiac*		*t*	*p*
	m	*s*	*m*	*s*		
Basal H I slope†	23.6	17.0	12.7	5.3	2.98	.01
Basal I J slope	21.1	8.8	15.3	7.5	2.35	.025
Exercise J amplitude‡	0.71	0.24	0.51	0.21	2.98	.01

*m and s: Sample means and standard deviations, respectively
†Slope in pounds per second
‡Amplitude in pounds (453 Gm. per pound)

significant differences between normal and cardiac means. Those which failed to achieve the 5 per cent level were then dropped from further processing. All of the *wave type* observations were in this category. Those variables which did yield significantly different results were combined in discriminant analyses in various groupings. From these secondary arrangements, particular variables were systematically dropped when their degree of correlation with others resulted in an inability to add important *independent* information to the discriminant analysis. This process was applied repeatedly until the variables reported in Table II were obtained. Measurements made on complexes in the full inspiratory phase of dynamic respiration yielded the strongest discriminators.

Frequency polygons showing the variables of Table II are presented in Fig. 3. Each of these shows a large overlap between the normal and cardiac samples. The existence of this overlap is entirely compatible with the significant "t" tests obtained, however, and demonstrates the important difference between the clinical concept of "diagnosticity" and statistical significance. In spite of a substantial degree of the latter property, it is clear from the frequency polygons that no one of these variables by itself would be very useful in classifying the two groups, i.e., separating normal subjects from cardiac patients. Improvement of this separation by the use of multivariate analysis is possible.

The variables of Table II were combined in a discriminant analysis. As described by Hoel, this procedure allows us to calculate easily a new variable made up of weighted contributions from each of the three individual measurements. This variable, called the "discriminant function," has the property of optimally separating the two groups through the use of the in-

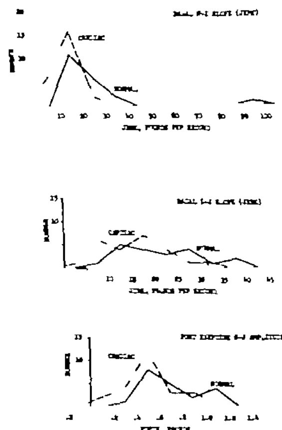


Fig. 3. Frequency polygons of the three BCG measurements used in discriminant analysis. Table II gives the statistical summary for these variables.

Dislodgment of a bullet from the sinus of Valsalva by cardiac catheterization

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Penetration of the heart or great vessels by a bullet may result in tamponade, sepsis, or injury to the coronary arteries or other cardiac structures. Twenty years ago Harken[1] emphasized the threat of delayed embolism posed by an intravascular foreign body and stressed the need for its removal. The following report demonstrates the value of selective angiocardiographic methods[2] in localizing precisely a foreign body within the heart or great vessels and documents the dislodgment of a bullet from the aortic root to a peripheral site by retrograde arterial catheterization.

Case report

A 31-year-old Negro, previously in good health, was admitted to the hospital shortly after he had been shot by his girl friend with a 22-caliber revolver. Examination revealed a small gunshot wound 2 inches to the left of the mid-sternal line in the second intercostal space. The blood pressure was 140/90 mm. Hg, and the physical findings of the heart and lungs were normal. Fluoroscopic study and roentgen films of the chest revealed slight cardiac enlargement with widening of the superior mediastinal shadow and a metallic foreign body that was believed to be lodged in the interatrial septum (Fig. 1).

Numerous subsequent x-ray films disclosed no change in the position of the opaque object. An electrocardiogram made at the time of admission of the patient demonstrated inverted T waves in Leads V. On the third hospital day, second-degree atrioventricular heart block with Wenckebach phenomenon was noted. The patient was given a 2 week course of Prednisone therapy, during which the rhythm gradually reverted to sinus with first degree heart block. On the nineteenth day a consultant suggested the possibility that the conduction disturbance had been produced by damage to the coronary arteries. During his examination a Grade 2 decrescendo, diastolic murmur was noted at the left sternal border in the third intercostal space. The blood pressure was 120/70 mm. Hg and the peripheral pulses were slightly bounding in character. Cardiac catheterization on the twentieth day demonstrated normal pressures in the pulmonary capillaries, pulmonary trunk, and aorta. The right atrial mean pressure and the right and left ventricular diastolic pressures were each elevated, respectively, to 10, 11, and 17 mm. Hg. Selective cineangiographic studies revealed patent coronary arteries and slight aortic insufficiency. The projectile was localized in the right sinus of Valsalva. During further manipulation of the tip of the catheter within the aorta, the operator was startled by the sudden liberation of the metallic object, which was watched fluoroscopically as it slowly migrated, pulsing with each heartbeat and ricocheting around the arch of the aorta—to the abdominal aorta. Here it pulsated for a moment in the vicinity of the right

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Fig. 1. Posteroanterior (A) and lateral (B) x-ray films of the chest demonstrate the bullet density.

eral artery as the patient was directed to turn from the left anterior oblique to the supine position and then it migrated gradually into the right femoral artery (Figs. 2 and 3A). The patient was completely free of any symptoms or signs of ischemia and, in fact, was totally unaware of the sequence of events (save for the expression of surprise that undoubtedly appeared on the face of the operator). A unsuccessful attempt was made that evening to extract the bullet surgically from the right femoral artery. A second x-ray film (Fig. 4) made on the following day demonstrated a more distal location of the density of the bullet which by then had probably lodged in the right profunda femoris artery. One year later the patient was still asymptomatic but a murmur persisted, which was consistent with mild aortic insufficiency. In the interim, he had undergone a second cardiac catheterization study in another hospital, and this had resulted in the same findings.

Comment

The precise localization of an intracardiac foreign body is essential for the accurate assessment of cardiac damage and the proper management of the patient. Barrett and Swan, Forsee and Goyette have indicated that a metal fragment, if chronically and securely embedded within the myocardium, need not be removed. On the other hand, when a metallic object has been implanted experimentally in such manner as to cause a cardiac valve to impinge upon it during each systole, erosion and eventual destruction of the valve cusp or leaflet result. In addition to its conventional use in diagnosis, cardiac catheterization may be beneficial in identifying the exact location of an intracardiac foreign body. The one previous report[3] that we have been able to find describing such use of a catheter is that of a child who had ingested a hairpin. On x-ray study the latter was seen within the cardiac silhouette; a catheter introduced by vein was advanced until it encircled the metallic density within the cavity of the right ventricle, from which it was successfully extracted at subsequent operation.

In the patient of the present report the detection of the bullet in the x-ray films of the chest initially raised the possibility of injury to a number of cardiac structures, such as the septa, valves, conduction system, and aortic root. The subsequent finding of a murmur of aortic insufficiency, although it might have been caused by a pre-existing abnormality, suggested that the aortic valve was injured and that the bullet lay partially in the cavity of the left ventricular outflow tract. Finally, the development of heart block implied injury to conduction tissue either as a result of direct damage or damage from ischemia due to interference with the coronary blood supply. By means of cineaortography, the foreign body was

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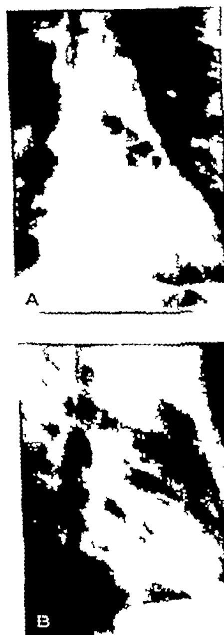


Fig. 1. Posteroanterior (*A*) and lateral (*B*) x-ray films of the chest demonstrate the bullet density.

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Fig. 2. Posteroanterior (A) and lateral (B) x-ray films of the chest taken immediately after arterial catheterization, during which the bullet was dislodged from the sinus of Valsalva.

perceived in the right sinus of Valsalva and mild aortic insufficiency was evident. By selective coronary cinearteriography the existence of direct trauma to the coronary vascular system was excluded. Had the procedure been terminated at this point, strong consideration would have been accorded the surgical removal of the



Fig. 3. X-ray film of the right upper femur. The bullet density has been dislodged from the sinus of Valsalva to the right femoral artery.

bullet from the aortic root both in order to prevent continuing trauma to the aortic valve cusps and to avoid potential arterial embolism with catastrophic results. Fortunately, the bullet was dislodged without complication by the tip of the catheter and came to rest in a branch of the right femoral artery where it has remained without causing symptoms. It is possible that an attempt to remove it by operation will be indicated in the future. In reviewing the medical literature since 1946, when clinical studies of the then new technique began to appear, we have not found a previous report of dislodgment of an intravascular bullet by cardiac catheterization.

Summary

The proper management of a patient with a retained intracardiac foreign body depends upon its precise localization and the accurate assessment of resulting cardiac damage. Cardiac catheterization with selective angiocardiographic studies provides a means for identifying both the exact location of the foreign body and the mechanism and extent of any cardiac dysfunction including trauma to a coronary artery. In addition, the case reported



Fig. 4. X-ray film of the right upper femur reveals a more distal location of the density of the bullet, hich now lies in the right prof nda femoris artery

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Review

Central nervous system mechanisms mediating cardiac rate and rhythm

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Although recent review articles by Lymas and Hoff, Kell and Carroll[2] emphasized the importance of cortical and subcortical mechanisms on cardiovascular function, little attention was focused upon changes in heart rate and rhythm mediated by these higher neural structures. This review will therefore be devoted primarily to a discussion of such cardiac alterations. Inclusion of the numerous experimental reports dealing with changes in activity in cardiac nerves by reflex or humoral stimulation, as well as those related solely to central regulation of arterial pressure, must be considered beyond the scope of this paper.

That electrical stimulation of the cerebral cortex can influence cardiac rate and rhythm was observed almost simultaneously by Schiff[3] and Danilewsky in the early 1870's. Within a few years these initial observations were more fully documented,[4] although concern was directed largely to alterations in vasomotor activity rather than heart rhythm.

A major contribution to our concept of central regulation of cardiac rate and rhythm can be attributed to Hunt's early work, which suggested that these variables were under the influence of reciprocal centers in the medulla oblongata—one exerting acceleratory and the other inhibitory influences. The former was considered to occupy those reticular structures that include the bulbar region, while the latter was believed to lie in close communication with the vagal nucleus. Furthermore, he hypothesized that accelerator impulses traveled in the sympathetic efferent outflow, whereas inhibitory fibers were located within the vagi. Credit, however, for the discrete localization of a center concerned with vasomotor control belongs to Dittmar[10] and Owsjannikow.[11] These investigators independently demonstrated by serial ablations in the pons and medulla in rabbits an area in the floor of the fourth ventricle which they believed to be essential in the maintenance of blood pressure. Subsequent work by Ranson and Billingsley[12] confirmed the existence of such a pressor region at the apex of the ala cinerea or fovea inferior and also localized a depressor region in the area postrema just lateral to the obex. Stimulation of the pressor area was also associated with slowing of the heart.

The studies by Hunt[8] also supported

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the hypothesis, formulated earlier by MacWilliam[12] that the accelerator nerves to the heart were under the dominant influence of vagal tonic inhibition Hunt was unable to obtain significant rate changes to electrical stimulation of the distal cut-ends of sympathetic ardiac nerves. Subsequent investigations by Hooker[1] and by Bainbridge[14] upheld the idea of vagal pre-eminence in the regulation of heart rate. In addition these investigators marshalled evidence to show that following bilateral section of the vagi the heart reached a maximum rate which was no longer amenable to further increase by either sympathetic or humoral influences. A series of studies by Tulgan[8-13] strongly supported these findings and led to the formulation of the so-called law of the physiological maximum state of the heart.

In a critical analysis of the aforementioned research Cannon and Lewis attributed the inability of these investigators to increase heart rate solely to the state of anesthesia of the organism They also demonstrated that the anesthetic agent increased the heart rate to a level below its maximum and there held it in such a manner as to make it unresponsive to direct or reflex stimulation They concluded therefore that the hypothesis of a physiological maximum state of the heart, so strongly supported for a quarter of a century was simply the result of an experimental artefact due to anesthetics.

The classical experiments by Karplus and Kreidl[18] demonstrating alterations in cardiac rate rhythm and systemic blood pressure on electrical stimulation of the hypothalamus stand as a landmark in drawing attention to the role of the diencephalon in the regulation of cardiovascular function

The influence of subcortical structures on cardiac rate was also shown by Bard[17] in his sham rage experiments In these studies, in which the cerebral hemispheres, corpora striata and the cranial half of the diencephalon were surgically ablated striking increments in heart rate were observed following decerebration these increases were abolished or markedly attenuated He conjectured that the mechanism mediating this response resulted from an enhanced discharge in the sympathetic cardiac nerves and he discounted the role of the vagi or adrenal glands.

By 1930 it was reasonably well established that cortical and subcortical regions of the brain exerted pronounced effects upon cardiac rate and rhythm Specific structures within these neural areas were however poorly delineated and the precise role of the autonomic nervous system in the mediation of these responses was not well understood About the same time Bard[19] voiced strong objections to the results of numerous studies in which electrical stimulation had been delivered to the brain He pointed out that many of the reported effects might conceivably be accounted for by a spread of stimulating current to distant neural structures, or by the production of seizure activity leading to widespread discharges. He further indicated that the methods utilized had failed to provide satisfactory evidence for sympathetic representation on the cerebral cortex. Bard was reluctant to ascribe significant autonomic influence to the cerebral cortex and it was his belief based on his own work on that of Karplus and Kreidl[18] and on certain studies related to temperature regulation[20-22] that the diencephalon was the major source of activation of the sympathetic division of the autonomic nervous system

Cerebral cortex It was imperative therefore to re-examine the basis of this controversy an effort which led to the re-establishment of electrical stimulation as a precise technique in neurophysiological investigation. The work of Hoff and Green[23] was of great significance in demonstrating that electrical stimulation of cortical structures caused selective depolarization of discrete regions and need not be associated with generalized seizure activity In cats, monkeys, and chimpanzees lightly anesthetized with ether and in some experiments curarized they demonstrated that electrical stimulation of the motor and premotor cortex evoked cardioacceleration with a concomitant pressor response They also showed that stimulation of the frontal cortex, in a region adjacent to the gyrus proreus, induced cardiac slowing with either no change or only a mild decrease in blood pressure furthermore these effects

were observed in animals that were both stellectomized and adrenalectomized, suggesting that the observed responses were mediated by the vagi. To support the hypothesis that the observed autonomic changes resulted from stimulation of discrete cortical loci, the authors noted that (1) pressor and depressor points were localized within 3 to 4 mm. of each other, (2) local anesthesia of the cortex to a depth of 3 mm. abolished the response, (3) isolation of a small responsive area of the cortex by undercutting eliminated all further effects from the region, and (4) excitation of the efferent fiber tracts in the white matter immediately below the cortex usually evoked a vasomotor response, while none could be elicited to stimulation of the descending tracts emanating from this region when they had degenerated as a result of previous ablation of the overlying cortex. These responses could not be attributed to seizure activity since they were elicited in the noncurarized preparation from which no muscular movement was observed.

Crouch and Thompson[27] studied the effects of electrical stimulation of the motor and premotor cortex in cats, dogs, and monkeys subjected to a variety of anesthetic agents. In cats and dogs, the stimulation of a relatively discrete region of the frontal cortex adjacent to the anterior sigmoid gyrus usually elicited autonomic responses. When an increase in heart rate was observed, it was always associated with a mild pressor effect, but when a slight depressor response was evoked, a concomitant decrease in heart rate was invariably seen. Minimal alterations in blood pressure were usually associated with minimal changes in rate. In monkeys, the changes were similar to those produced in both cats and dogs but were observed in response to stimulation of wider areas of the brain; however, motor and premotor regions were most reactive. Isolation of the motor from the sensory cortex by means of deep cortical incisions failed to abolish the weak reactions obtained by stimulation of the latter, which suggests that fibers from the sensory region projected directly to the hypothalamus. Since other autonomic effects could also be evoked, Crouch and Thompson hypothesized that the cortex exerted a global rather than discrete autonomic influence. They also observed species differences. For example, in cats and monkeys the effects were predominantly sympathetic, whereas in dogs they were largely parasympathetic. Although responses were always observed in both the anesthetized and curarized preparation, they were suppressed in the very deeply anesthetized animal, regardless of the agent used. It should be pointed out, however, that selective interruption of either division of the autonomic nervous system was not attempted and that the speculation of Crouch and Thompson concerning mechanisms was entirely inferential. Hsu and his associates[29] stimulated the sigmoid gyrus of dogs anesthetized with chloralose and reported increases in heart rate averaging 20 per cent above control levels. It is noteworthy that the vasomotor responses elicited by cortical stimulation in these experiments were predominantly of a depressor type, in marked contrast to the results reported by Crouch and Thompson.[27] Dusser de Barenne and Kleinknecht[28] also reported depressor responses to electrical stimulation of the motor cortex in dogs, cats, and rabbits. These discordant results might be attributed to species differences in cortical representation or to the anesthetic agents used.

The important influence of the frontal lobes on autonomic function was demonstrated by Kennard[1] in her classic ablation studies. By surgical removal of the frontal lobes in cats, she was able to produce "sham rage," with all its manifestations, associated with significant increases in heart rate. This response pattern was never observed after extirpation of the parietal or occipital lobes provided the frontal lobes were left intact. Ablation of the orbital cortex produced the typical sham rage response but without the spasticity which was seen after bilateral frontal lobectomy. Destruction of the orbital surface of the frontal lobes, however, produced a sham rage response analogous to that observed after the bilateral ablation of the frontal lobes. In an earlier paper, Kennard[30] had reported a decrease in heart rate upon electrical stimulation of the premotor cortex in monkeys. The extensive experiments by Lund[31] further confirmed the importance

of the anterior third of the brain including the anterior sigmoid process and posterior sigmoid and coronal gyri in the regulation of autonomic function.

Limbic system. For many years the forebrain areas designated by Broca[33] as the *grand lobe limbique* were believed to be concerned primarily with olfaction. In 1937 Papez[34] included most of these structures in an anatomical circuit which he proposed as a mechanism of emotion. Many subsequent reports[35-40] have confirmed and extended these observations and thus fact leads us to a modification of Papez's early proposal. In using the term *limbic system* today many investigators would include besides the cingulate and hippocampal gyri the hippocampus and the orbitoinsulo-temporal polar regions—the cell stations which have been shown to be associated with the "limbic lobe" (for example the amygdaloid complex septal nuclei hypothalamus, anterior thalamic nuclei regions of the basal ganglia and certain midbrain structures).

The numerous earlier studies demonstrating the influence of the cerebral cortex upon cardiac rate and rhythm and upon autonomic function in general had been concerned primarily with stimulation of the areas on the surface of the brain. In a more recent series of experiments Delgado and associates[41-43] have shown that electrical stimulation of the "hidden motor cortex" which includes regions buried within the presylvian, coronal and cruciate sulci exerts important autonomic influences in addition to its known motor effects. Experiments in this series were performed on unanesthetized cats, monkeys, and human subjects, and included electrical stimulation of the motor cortex subiculum posterior hippocampus, and substantia nigra. Excitation of the motor cortex in the monkey evoked modest increases in heart rate with concomitant pressor effects. During these responses there were no observed changes in electrical activity recorded from either the stimulating points adjacent motor areas or thalamic nuclei. Although the heart rate was moderately increased changes in rhythm were never observed on stimulation of the motor cortex. It is particularly noteworthy that after-discharges elicited by intense stimuli leading to diffuse seizure activity had no effect whatsoever upon either heart rate or rhythm. These data strongly support the hypothesis that autonomic responses may be evoked by electrical stimulation of discrete cerebral areas and furthermore, that these effects need not be related to after-discharges.

Studies involving stimulation of the orbital cortex have been carried out by a number of investigators.[44-46] Although a variety of autonomic responses have been recorded during the stimulation of this region few data are available on cardiac rhythm disturbances. It is interesting to note that, as early as 1894 Spencer[46] observed a marked decrease in heart rate on electrical stimulation of an area of the orbital gyrus, the excitation of which also produced respiratory inhibition. The heart rate response was considerably less pronounced in the monkey. More recently Chapman and his associates[47] studied responses to electrical stimulation of this same area of the brain in patients undergoing prefrontal lobotomy for serious psychiatric disorders. They observed elevations in systemic blood pressure associated with slowing or arrest of respiration during stimulation of the posterior half of the orbital gyrus. In these experiments, however alterations in cardiac rate were negligible.

Delgado and co-workers[42,43] recently studied the effects of seizure activity following the electrical stimulation of the orbital cortex as well as other cortical and subcortical structures. They showed that stimulation of the orbital cortex in the cat elicited localized after-discharges accompanied by convulsive activity usually restricted to the contralateral side of the face. Heart rate was not modified during orbital stimulation although the blood pressure elevation was followed by bradycardia during its return to control level. Excitation of the orbital cortex with intensities just below after-discharge thresholds had no effect upon blood pressure. The vasomotor response observed in these experiments appeared to be dependent upon seizure activity. It might be mentioned that neuroanatomical projections have been demonstrated from the orbital gyrus to the supraoptic nuclei paraventricular

nuclei and ventromedian nuclei of the hypothalamus.

The *anterior portion* of the cingulate gyrus is known to exert powerful influences upon the autonomic nervous system. In 1945 Smith[illegible] stimulated this region in *monkeys* and induced a variety of severe cardiac arrhythmias as well as other autonomic effects. Although bradycardia and cardiac arrest were frequently associated with respiratory arrest, it was apparent that the former was not dependent upon hypoxia resulting from the latter since the cardiovascular effects of stimulation were still present in the curarized and artificially ventilated preparation. That cardiac inhibition was due to vagal efferent discharge was supported by the finding that bilateral vagotomy abolished the cardio-inhibitory response. In a subsequent study Ward confirmed these results.

Pool and Ransohoff[illegible] selectively stimulated regions of the rostral cingulate gyrus in psychotic patients undergoing prefrontal lobotomy. They noted that the pulse rate increased in 3 patients with a maximum rise of 40 beats per minute. In 7 patients, decline in pulse rate was recorded with a maximum decrease of 40 beats per minute. Although no electrocardiographic tracings were available, the pulse by palpation was slow and grossly irregular. Inasmuch as the descending projections from the cingulate gyrus mediating these responses are rather fully unknown, a pathway to the anterior temporal lobe and amygdaloid complex has been suggested by Wall and Davis.[illegible]

A number of studies attest to the importance of the temporal lobe in cardiovascular function.[illegible] Anand and Dua,[illegible] using a variety of stimulus parameters, observed both increases and decreases in heart rate on stimulation of the amygdala, hippocampus, anterior cingulate gyrus and temporal polar regions but they failed to localize specific sympathetic and parasympathetic points. On the other hand while recording the electrocardiogram Delgado and his associates[illegible] stimulated the subiculum and hippocampus in monkeys. They produced atrial ectopic complexes associated with frequent sinus pauses and with higher stimulus intensities also induced ectopic ventricular rhythms. The evoked responses were consistent and occurred in the absence of after-discharges or seizure activity. In a later study, Porter and his colleagues[illegible] stimulated areas of the medial temporal lobe including the dentate gyrus, subiculum, hippocampus and medial nucleus of the amygdala and induced bursts of ectopic ventricular activity both singly and in trains. Cervical transection of the spinal cord which followed induction of these arrhythmias resulted in a return to sinus rhythm within 10 to 15 seconds. Recently, Reis and Oliphant[illegible] have shown in chronically prepared unanesthetized monkeys that both bradycardia and tachycardia could be elicited by stimulation of the amygdaloid complex. These responses were associated with neither blood pressure changes nor motor activity. These investigators also observed cardiac arrhythmias including sinus arrhythmia, sinoatrial depression, ectopic atrial contractions, intermittent heart block, nodal escape and premature ventricular contractions. Either atropine or bilateral vagotomy abolished the supraventricular arrhythmias. It is of interest that the experimentally induced ventricular extrasystoles could not be abolished by bilateral section of the vagi. We suggest that this response was mediated by enhanced sympathetic discharge. Studies from our laboratories[illegible] which will be described later support this hypothesis. Reis and Oliphant further inferred that the vagally induced alterations in cardiac rate and rhythm were mediated by the amygdalovagal pathway, whereas sympathetic effects were transmitted via more direct pathways such as the temporo-hypothalamic or temporotegmental. It should be pointed out that in these experiments bradycardia was correlated with the production of after-discharges, whereas no such relationship existed for tachycardia.

In cats immobilized with gallamine triethiodide Hockman and Mauck[illegible] recently observed that electrical stimulation of points in the basal amygdaloid nuclei elicited sinus tachycardia associated with marked elevation in arterial blood pressure in contrast to the report by Reis and Oliphant[illegible] who observed only mild pressor responses which were inconsistently related to increases in heart rate. In some experi-

ments, a stimulus of 0.5 Ma. produced a sinus tachycardia which was followed by ventricular premature contractions in bigeminy at the stimulus offset. In other studies an increase in stimulus intensity induced ventricular tachycardia which persisted after cessation of stimulation and was followed by ventricular premature contractions prior to a return to normal sinus rhythm.

In recent studies in human subjects, Van Buren[47] delivered electrical stimuli to mesial temporal structures. He observed tachycardia and in one instance bradycardia associated with automatisms. He further noted considerable variability in the observed response, and suggested that this neural region participated in the integration of responses rather than served as a center of sensor motor representation.

Diencephalon. Since the classic studies of Karplus and Kreidl[48] hypothalamic influences on cardiovascular function have been clearly recognized. These workers stimulated the area behind the optic chiasm lateral to the infundibulum and observed changes in heart rate associated with elevations in blood pressure. A few years later Schrottenbach[49] produced alterations in heart rate following experimental diencephalic lesions. Inasmuch as these early investigations set the stage for subsequent work in this area, the first major contribution demonstrating production of cardiac arrhythmias by stimulation of the hypothalamus must be attributed to Beattie, Brow, and Long[50] in 1930. Working with cats these investigators observed that anesthesia induced with chloroform evoked abnormal heart rhythms which they considered to be the result of either enhanced sympathetic activity or the release of epinephrine. They also found that experimental lesions in the posterior hypothalamus abolished these abnormal complexes, while destruction of the anterior hypothalamus was without effect. The arrhythmias which they elicited to electrical stimulation of the caudal portion of the hypothalamus were similar to those induced by chloroform anesthesia and were unaffected by removal of the adrenal glands. Atrioventricular conduction time was consistently shortened by stimulation of this latter region. Since the effects observed following destruction of the posterior hypothalamus differed from those produced by removal of the anterior hypothalamus Beattie[4] hypothesized that these two diencephalic areas possessed opposite functional characteristics, the former evoking sympathetic and the latter parasympathetic responses. He believed that these two regions did not function as discrete "centers." In a similar series of experiments, Allen[51] stimulated the hypothalamus in rabbits and evoked ventricular premature contractions. Van Bogaert,[52] who monitored the electrocardiogram continuously during stimulation, also reported both tachycardia and bradycardia as well as certain cardiac arrhythmias including nodal rhythm, atrioventricular dissociation and ventricular arrest.

The most painstaking and detailed studies of the hypothalamus by the electrical stimulation method are perhaps those of Ranson, Kabat and Magoun.[53, 54] They explored the hypothalamus and its adjacent areas, millimeter by millimeter, and correlated experimentally elicited responses with precise stimulation points as determined by histological section. They demonstrated that electrical stimulation of the hypothalamus, particularly the full extent of its lateral and posterior regions, evoked mainly sympathetic responses. In contrast to Beattie's[4] findings, they were unable to obtain parasympathetic responses to stimulation of the anterior hypothalamus. Although Ranson and his associates reported modest increases in heart rate and rarely bradycardia, they did not mention seeing striking alterations in either rate or rhythm. It would appear that absence of careful electrocardiographic monitoring was perhaps a factor in their failure to observe certain cardiac rhythm disturbances.

In another significant paper Magoun and his associates pointed out that adrenergic substances are indeed released into the circulation by hypothalamic stimulation, but that the prolonged-response latencies indicate that the effects of electrical stimulation are due to direct neural influences. Morison and Rioch[55] and Magoun[71] showed that cardiovascular sponses are mediated by projections the hypothalamus which are inde

of descending pathways from the cerebral cortex

Although electrical stimulation has been established as a highly selective experimental method for the elicitation of neural responses, chemical and mechanical stimulation in addition to surgical ablation have also been commonly utilized. In an early paper Cushing[12] injected Pituitrin into the cerebral ventricles and suggested that the dominantly parasympathetic responses which he observed were mediated by diencephalic nuclei. This hypothesis was based upon two major facts: (1) that the responses were abolished by prior injection of atropine and (2) that the effector responses failed to occur in the presence of lesions which destroyed or severely impaired diencephalic regions. Dikshit[13] injected acetylcholine, nicotine, and caffeine into the lateral ventricles of cats and elicited a number of cardiac irregularities including ventricular premature contractions. These changes occurred without significant alterations in arterial pressure or respiratory rate, and they were unaffected by bilateral vagotomy. Although the author suggested that these responses were mediated by the hypothalamus, the experimental data failed to rule out other possible neural pathways.

The studies of the diencephalon so far reviewed indicate, in a general manner, the type of responses to be expected from electrical stimulation of hypothalamic and other subcortical regions; however, they yield essentially no information concerning related changes in activity in peripheral nerves. A major contribution to this area of research, as well as to our understanding of neural transmission in autonomic fibers, must be attributed to the classic studies of Pitts and his colleagues.[?] They recorded impulses in peripheral sympathetic trunks during stimulation of the hypothalamus and correlated this activity with observed physiological responses. Electrical stimulation of the hypothalamus elicited an almost instantaneous (<0.1 second) increase in activity recorded from the inferior cardiac nerve. This discharge ceased immediately at the offset of the stimulus, although blood pressure remained elevated for a somewhat longer period. The delay in fall in blood pressure was ascribed to inertia of the effector system and not to sympathetic after-discharge. An increase in the frequency of impulse discharge in the inferior cardiac nerve was observed when the intensity of the hypothalamic stimulus was increased. When the anatomic placement of the electrode was changed, the intensity of the response in the peripheral nerve was altered. Furthermore, the investigators observed a close relationship between the rate of activity in cardiac nerves and the frequency of hypothalamic stimulation; as the frequency of the stimulus varied from 10 to 100 c.p.s., the occasional discharge developed into a regular firing pattern; when the stimulus reached its maximum frequency, a maximum of six spikes per second was observed.

In more recent studies involving hypothalamic stimulation, investigators have made use of continuous electrocardiographic monitoring and have selectively interrupted both divisions of the autonomic nervous system either by transection of the spinal cord or by vagotomy. Such studies have permitted a more detailed description of abnormalities in cardiac rhythm and have identified the division of the autonomic nervous system subserving a particular response. Weinberg and Fuster[14,15] performed a series of experiments on cats, immobilized with gallamine triethiodide, in which electrodes were stereotaxically lowered into diencephalic regions. They observed that most ECG changes were evoked by electrical stimulation of the posterior and lateral areas of the hypothalamus. Wave components, rate, rhythm, and pacemaker location were found to be susceptible to change by central stimulation. The most frequently observed abnormality on stimulation of the posterolateral hypothalamus proved to be ventricular tachycardia, whereas atrioventricular dissociation was rarely noted. These investigators pointed out that, with initiation of hypothalamic stimulation, a ventricular pacemaker may alternate with the sinus node pacemaker to produce a trigeminal rhythm; later, with continued stimulation, the ventricular pacemaker may subsequently alternate with another ventricular focus or actually usurp the rhythm entirely, thus leading to ventricular tachycardia. At times they observed trigeminy and quadri

geminy. In general, a marked alteration in impulse formation in the sinus node, as manifested by P wave change or atrial extrasystoles or both, was uncommon. In certain instances, stimulation of the posterior hypothalamus produced a narrowing of the PR interval, widening of the QRS, and inversion of the T wave; this pattern occurred in alternating sequence or with every fourth beat. Many of these abnormal complexes exhibited a configuration quite similar to the Wolff-Parkinson-White (WPW) pattern seen clinically. Weinberg and Fuster maintained that the posterior hypothalamus exerted an activating influence upon the sinus node, whereas the lateral hypothalamus and subthalamus exerted a dominant tonic influence upon the myocardium. Nodal rhythm always appeared late during the stimulation period or followed its cessation. They believed that this latter arrhythmia was most likely the result of reflex vagal inhibition of the sinus pacemaker and, therefore, considered it to be a passive ectopic rhythm. Attar and his associates,[72] using similar techniques in a series of experiments with cats but with chloralose as the anesthetic agent, induced a mild bradycardia and pressor response to stimulation of the anterior hypothalamus. They also evoked transitory A-V dissociation and multiple ventricular premature contractions. Stimulation of the posterior hypothalamus elicited A-V nodal rhythms, aberrant ventricular conduction, multifocal ventricular premature contractions, and, in some instances, fusion contractions. In neither of the preceding studies was selective interruption of autonomic efferent outflow attempted, and thus no data are available as to the division of the autonomic nervous system mediating these effects.

Recently Melville and associates[41] stimulated anterior, lateral, and posterior areas of the hypothalamus in cats with selective interruption of both divisions of the autonomic nervous system. Although tachycardia and ectopic contractions elicited from these sites in the intact animal were abolished by transection of the spinal cord at the level of the second cervical vertebra, the majority of these arrhythmias were also attenuated by bilateral section of the vagi with the sympathetics intact. Furthermore, they observed, in contrast to others,[14,46] that the anterior hypothalamus produced more arrhythmias than its posterior component.

Manning and Peiss[42] were able to demonstrate in vagotomized cats immobilized with d-tubocurarine or anesthetized with chloralose vasoconstriction, myocardial augmentor, and cardioaccelerator responses to hypothalamic stimulation. Although these responses did occur singly more frequently, they tended to occur in combination. The regions most reactive in evoking these responses were the lateral and posterior hypothalamus and a portion of the subthalamus. In subsequent experiments, Manning and his associates[43,44] stimulated the posterior hypothalamus and elicited a variety of electrocardiographic changes including sinus tachycardia, ventricular premature contractions, bigeminal rhythm, A-V dissociation, and ventricular tachycardia. These arrhythmias were most frequently observed following the termination of the stimulus. The abnormal complexes disappeared upon cooling of the vagi and reappeared upon rewarming of these nerves. They were also abolished by bilateral vagotomy or extirpation of the stellate ganglion. Electrical stimulation of the distal cut-end of the right vagus nerve slowed the sinus rate, and electrical stimulation of the right stellate ganglion elevated sinus rate but never produced arrhythmias. These investigators reported that simultaneous stimulation of the vagus and stellate evoked arrhythmias similar to those observed to diencephalic activation. They interpreted their data to indicate that the arrhythmias induced by diencephalic stimulation were the resultant of both sympathetic and parasympathetic influences upon the heart. The experiments by Parker and his associates,[49] who reported WPW-like complexes on stimulation of the posterior hypothalamus, fail to support the conclusions drawn by Manning and Peiss. They pointed out that the arrhythmias which they observed resulted from vagal-induced migration of the pacemaker toward and beyond the A-V node.

In the wake of the controversy engendered by these contradictory results, Mauck and his colleagues[45-48] began a series of studies, the object of which was to delineate

cerebral structures influencing heart rate and rhythm and to elucidate the role played by both *divisions of the autonomic* nervous system in the mediation of experimentally induced cardiac alterations. In adult beagle dogs lightly anesthetized with thiamylal sodium, Hockman and his associates delivered precisely controlled stimuli to diencephalic and mesencephalic *loci previously shown to elicit sympathetic* responses. Electrical stimulation of points in the central gray substance and reticular formation of the midbrain and the ventromedial region of the hypothalamus elicited a spectrum of ectopic ventricular rhythms always accompanied by striking elevations in systemic *blood pressure. Observed in* sequence were sinus tachycardia, ventricular fusion contractions, ventricular premature contraction (which were frequently multifocal and coupled to the preceding normal sinus complex in bigeminal and trigeminal patterns), ventricular tachycardia, and *in some experiments*, ventricular fibrillation. Following offset of a stimulus there was a reversal of the sequence outlined. When a mild stimulus evoked sinus tachycardia, modest increments in intensity would induce the complete spectrum. Ventricular fusion *complexes which fulfilled the criteria of* the Wolff-Parkinson-White electrocardiographic *configuration frequently preceded* the return to normal sinus rhythm. Bilateral section of the vagus nerves had no influence upon the spectrum of abnormal complexes; however, electrical stimulation had no observable effect on normal rhythm following intravenous administra*tion of propranolol.* They concluded that the abnormal rhythms observed were mediated exclusively by the sympathetic division of the autonomic nervous system. In a subsequent study, *Hockman* and Mauck induced in both dogs and cats, the same spectrum of ventricular arrhyth*mia* of sympathetic origin by electrical stimulation of diencephalic and mesencephalic *structures. In these latter experi*ments the cats were immobilized with gallamine triethiodide.

Mesencephalon. In contrast to cortical diencephalic and bulbar regions, mesen*cephalic* influences on autonomic regulation have received scant attention. In a recent review, Uvnas drew attention to the paucity of information available concern*ing midbrain function* and *alluded to the* difficulties encountered in any attempt to differentiate between responses resulting from activation of primary neuronal elements and those caused by stimulation of fibers passing through the region. Bard and Macht[37] presented evidence in support *of at least one autonomic response mediated* by structures within the midbrain. They demonstrated in chronically decerebrate cats that animals with the brainstem transected through the rostral portion of the mesencephalon were capable of exhibiting a rage reaction accompanied by signs *of vigorous sympathetic activity. Although* this behavior did not resemble the well-integrated response observed in the cat with an intact hypothalamus, it was not so fragmented as that seen following more caudal sections at collicular and pontine levels. Studies of the role of the midbrain *in the regulation of cardiovascular function* have been for the most part carried out as extensions of experiments involving the diencephalon and few data are available identifying the division of the autonomic nervous system mediating responses from this area. For example, Kabat and colleagues *stimulated points caudal to the* superior colliculus including the central gray *substance and tegmentum and* although they observed striking alterations in blood pressure, noted little change in heart rhythm. Ueda and his associates, in contrast, observed that electrical stimulation of the central gray stratum and the reticular formation of the midbrain, as well as other *subcortical structures,* frequently elicited marked tachycardia. In addition they observed ventricular *prema*ture contractions which were considered to be of two distinct types: one appeared rapidly with stimulation as the result of direct activation of the sinus node pacemaker, while the other followed acute elevation of blood pressure after a significant latency *period. Ventricular premature con*traction of the first type were restricted *to stimulation of the median portion of* the brain stem. Other investigators, whose work has already been discussed, also reported significant rhythm disturbances on stimulation of the midbrain.

As mentioned previously, Manck and his associates[44-46] elicited a spectrum of ventricular arrhythmias by stimulation of diencephalic and mesencephalic regions in both dogs and cats. One of these studies[44] was devoted exclusively to the midbrain. In these experiments, the ventricular fusion contraction which resembled the WPW complex was investigated. Electrical stimuli delivered to the midbrain reticular formation at the level of the pons elicited alternated ECG complexes which were characterized by a shortened P-R interval, a widened QRS complex, constant P-P and R-R intervals, the presence of a delta wave, and a P-S interval identical to that seen in the normal complex. Although other arrhythmias were observed in this study, a precise analysis of these complexes was not carried out at that time. Bilateral section of the vagosympathetic trunks had no effect on the WPW-like complexes; this response was totally abolished by transection of the spinal cord at the level of the second cervical vertebra. It was also possible to abolish the abnormal ventricular component of this ECG complex by electrical stimulation of the distal cut-end of the right vagus with a stimulus of sufficient intensity to produce total sinoatrial arrest. This indicated that the aberrant ventricular response was most likely dependent upon impulses arising from within the sinoatrial node.

Myelencephalon. Although the bulbar region of the brain is considered by many investigators to be the site of a cardioaccelerator center, the evidence for this hypothesis, until quite recently, was based largely on analogy resulting from the demonstration of a vasomotor center residing in the rostral portion of the medulla oblongata, activation of which was associated with changes in heart rate[52, 53] or from indirect data derived from studies on heart rate changes induced reflexly via inhibitory and accelerator nerves.[7, 54, 57] Direct stimulation of the pons or medulla oblongata has virtually never been reported to increase or decrease the heart rate independently of blood pressure alterations.

Recently, a controversy has arisen with regard to the presence or absence of a discrete bulbar cardioaccelerator center. Peiss[58] stated unequivocally that, in vagotomized cats anesthetized with pentobarbital, he was unable to elicit significant short latency increases in heart rate by electrical stimulation of the dorsal medulla, although marked vasomotor and cardiac augmentor responses could be easily obtained. In the ventrolateral medulla, however, short latency accelerator responses were easily evoked accompanied by only mild pressor effects. Interestingly, under chloralose anesthesia, stimulation of the dorsal medulla produced a marked cardioacceleration which was partially or totally eliminated following electrolytic lesions within the hypothalamus. Thus, he seriously questioned the existence of an independent cardioaccelerator region within the dorsal medulla. In contrast, Chai and Wang[59, 60] performed an extensive series of experiments in which they stimulated the dorsal portion of the lower pons and medulla in vagotomized cats anesthetized with chloralose and decerebrated at the mid-collicular level and observed marked cardioacceleration with concomitant pressor responses. Stimulation of the ventrolateral medulla with a slight increase in stimulus intensity also evoked comparable changes. Responses to stimulation of the medulla on the right side most frequently elicited a marked tachycardia with only slight or moderate augmentation of cardiac contraction, whereas the left was characterized by marked augmentation with only moderate increases in heart rate. They further showed that the response evoked by stimulation of the dorsal medulla was not affected by ablation of the hypothalamus. The use of pentobarbital failed to abolish these effects in contradiction to the results reported by Peiss.[58] These data lend support to the concept that integration of basic cardiovascular function can occur at the level of the brain stem without the need of an intact diencephalon. The evidence, further more, favors a relationship between cardiac augmentation and cardioacceleration—a fact clearly demonstrated by Amoroso[61] in an earlier study in which he made sequential transections of the medullary pressor region and observed equivalent reductions in blood pressure and activity in the inferior cardiac nerve which led to cardioacceleration.

The role of the bulbar region on inhibi

tion of cardiac function has recently been reappraised. In a series of experiments with cats anesthetized with chloralose, Calaresu and Pearce[29] recorded unit activity from the dorsal motor nucleus of the medulla and single fibers of the cervical vagi simultaneously. Only rarely were significant increases or decreases in spontaneous activity observed at either site with intense reflex bradycardia induced by carotid occlusion. In those instances in which increased activity was observed in central and peripheral units, a temporal discrepancy existed between the onset of activity within the two units in relation to the onset of bradycardia. The investigators suggested that either the vagal cardioinhibitory pathway comprised very few fibers or that the cardioinhibitory cells were dispersed and few in number or not located within this medullary nucleus. Gunn and Sevelius[60] recently confirmed the absence of cardioinhibitory effects, including bradycardia, with direct stimulation of the dorsal motor nucleus in cat and to a lesser degree in dog. In a subsequent study, Calaresu and Cottle[61] found axonal degeneration in the intramedullary rootlets and in the cervical trunk of the vagus in cats with lesions of the dorsal nucleus of the vagus. They concluded that a direct connection does exist between the dorsal nucleus and the cardiac branches of the vagus, but the destination of such fibers has not been established. Furthermore, the scarcity of such fibers raised the possibility of an additional medullary region projecting to the pacemaker. In another study in this series Calaresu and Pearce[62] reported that stimulation of points in the tractus and nucleus solitarius produced bradycardia; however, they were unable to locate axonal degeneration in the intramedullary rootlets of the vagus in animals with lesions in the dorsal region of the nucleus of the tractus solitarius.[15]

Conclusion

It will have become apparent to the reader that the complex functional interconnections between different regions of the brain leave only a descriptive anatomical significance to the classical arbitrary divisions and that the designation of certain neural areas as "center" imposes severe limitations upon any attempt to understand the integrative action of the nervous system as a whole.

It will also have become obvious that certain controversial data are indeed difficult to interpret. While conclusions reached by a given investigator might lend support to one side of an argument, they seldom explain contradictory results to the satisfaction of all concerned. Methods employed by different workers often make a direct comparison of their findings an almost impossible task. Such variables as species, type and depth of anesthesia, stimulus parameters, and recording procedures underlie the difficulties involved.

Few researchers in this area would deny the importance of working with unanesthetized preparations, and present instrumentation is such as to make this approach eminently feasible. With available techniques, we can alter the environment of the freely moving animal with suitable devices (for example, telemetry), we can monitor a host of variables including blood pressure, heart rate, blood flow, temperature, and electrical activity from different levels of the central nervous system. The valuable information to be gained by studying an organism in continuous interaction with its environment is indispensable in any assessment of neural regulation of function.

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Fundamentals of clinical cardiology

Pulmonic valvular insufficiency: Etiology, recognition, and management

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Pulmonic valvular insufficiency is not an unusual lesion but as an isolated finding it is uncommon. The causes of pulmonic valvular regurgitation may be divided into three groups: (1) congenital, (2) acquired, and (3) functional.[1] The diagnosis of pulmonic insufficiency depends on the presence of a characteristic murmur. The clinical diagnosis may be confirmed by using various graphic techniques and cardiac catheterization.

Etiology

Once a diagnosis of pulmonic valvular insufficiency is made, determination of the cause depends on a properly taken case history to determine when the murmur was first noted and a thorough physical examination to evaluate any associated findings. Further work up may be needed to determine whether any other lesions are present. Only by a thorough evaluation can one establish a satisfactory etiological basis.

Congenital. Isolated congenital pulmonic valvular insufficiency is an uncommon lesion. In 1,000 cases of congenital heart disease reviewed by Abbott[2] there were eight cases of pulmonic insufficiency. Of these eight cases, two were secondary to anomalies of the pulmonic valve cusps. The remaining six cases had normal valves but had idiopathic dilatation of the pulmonary artery. The first two cases of isolated congenital pulmonic valve insufficiency described clinically were reported by Kaplan and associates[3] in 1953 and by Keith and associates[4] in 1955. Recently Nemickas and associates[5] reviewed the literature and were able to find clinical reports of 27 cases and added 4 of their own.

Congenital pulmonic valve insufficiency may be due to a hypoplastic, aplastic,[6-11] or bicuspid[12,14] valve. Congenital absence of the pulmonary valve may occur as an isolated lesion[6,15] or, as is usually the case, in association with other congenital heart lesions, especially tetralogy of Fallot.[7,9,15] A congenitally bicuspid valve may also be found as an isolated lesion,[12,1] but it is usually associated with either a ventricular septal defect or pulmonary stenosis or both.[14] Diamond and Lin[1] in an article on

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pulmonic stenosis, described three patients with associated pulmonic insufficiency murmurs, one of whom had cardiac catheterization findings suggestive of pulmonary valvular regurgitation. These cases probably represent examples of bicuspid valves with stenosis and insufficiency. Supernumerary cusps of the pulmonic valve have been reported to cause regurgitation.[7] The extra cusp may be deformed and fenestrated or may be normally shaped. In the latter instance the extra cusp may be either larger or smaller than the remaining cusps. There may be more then one extra cusp present. Idiopathic dilatation of the pulmonary artery has been noted to be associated with the murmur of pulmonic insufficiency[3,14-22] and with normal valvular cusps. However since this entity is a benign condition pathological material is limited.

The prognosis of *congenital pulmonic* valvular insufficiency as an isolated lesion is generally good although reports of follow up studies are limited. Kissin[7] in his review of 152 cases of supernumerary pulmonic valve cusps which were noted as an incidental finding at postmortem examination stated that in no instance could death be attributed to the presence of the anomaly. Generally the prognosis of absent or hypoplastic pulmonary valves depends on the associated cardiac anomaly.[23] There are rare case reports of newborn infants dying in congestive heart failure with isolated absence of the pulmonic valves.[9,10]

The pathological antomy of the pulmonic valve in the vast majority of the clinically reported cases of isolated pulmonic valvular insufficiency is not known. The patients previously described in the literature have been asymptomatic or have had minimal symptoms[3] In the case reported by Marshall and Jones[24] the *pulmonary insufficiency* was well tolerated with no evidence of cardiac decompensation in spite of the presence of thyrotoxicosis.

In the clinical setting of bronchopulmonary disease, complicated by pulmonary hypertension right-sided heart failure is more likely to develop.[12,13,25,26] Dickens and associates[13] and Ford and associates[14] each described a patient with isolated congenital bicuspid pulmonary valve and pulmonary regurgitation complicated by pulmonary emphysema and fibrosis. Both patients developed severe right-sided heart failure.

Although it is a benign lesion isolated incompetence of the pulmonic valve may lead to right ventricular hypertrophy[2,27,28] and as mentioned above may rarely lead to congestive heart failure. Experimental production of pulmonic valve insufficiency in dogs has been well tolerated.[29-32] In only one study did 1 dog out of 15 develop congestive heart failure.[31] In all the other studies there was no evidence of failure or limitation of activity. The right ventricle usually revealed mild to pronounced hypertrophy with dilatation.[29-31]

The only form of treatment recommended has been the use of appropriate antimicrobial prophylaxis at time of dental or surgical procedures.[21,28]

The following case report presents a typical example of congenital pulmonic valvular insufficiency.

PATIENT 1 (QHC 06 98 12). A 15-year-old schoolgirl was admitted on June 28, 1966, to the Queens Hospital Center for evaluation of a cardiac murmur. The patient, an only child, was the product of a normal, full-term spontaneous delivery. A murmur noted at birth had persisted until the present. Growth and development had been normal and there was no history of major illness or rheumatic fever. The patient was entirely asymptomatic.

During the physical examination, the positive findings were limited to the cardiovascular system. The blood pressure was 110/70 mm. Hg and the pulse rate was 70 per minute and regular. There was no cyanosis or clubbing. The point of maximum impulse was felt in the fifth left intercostal space at the midclavicular line. A slight left parasternal lift was palpable and a diastolic thrill localized to the second and third left intercostal spaces was felt. The first heart sound was normal. The second sound was widely split and failed to close during expiration. A grade 1/6 systolic ejection murmur and an early to mid, harsh crescendo-decrescendo diastolic murmur was localized over the second and third left intercostal spaces. The rest of the examination was within normal limits.

The electrocardiogram (Fig. 1) was normal. A vectorcardiogram (Fig. 2), made with the Frank lead system (tall leading), demonstrated increased anterior forces suggestive of right ventricular hypertrophy. The chest roentgenogram (Fig. 3) and cardiac series were normal. There was no evidence of dilatation of the pulmonary artery. The phonocardiogram (Fig. 4) documented the auscultatory findings and demonstrated wide splitting of the second sound (0.04 to 0.05 seconds) with only minimal respiratory movement. The amplitude of the aortic component was greater then the pulmonic

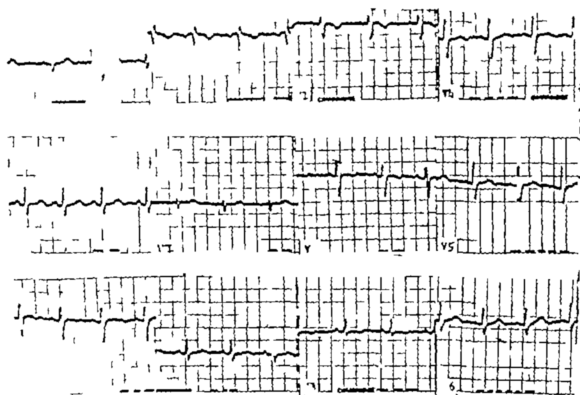


Fig 1 Electrocardiogram of Patient 1

Table I Summary of data obtained at cardiac catheterization (pressures in mm Hg)

Site	Patient 1		Patient 2		Patient 3	
	Systolic/ diastolic	*Mean*	*Systolic/ diastolic*	*Mean*	*Systolic/ diastolic*	*Mean*
Right atrium	—	0	—	3	—	0
Right ventricle	23/4	—	33/6	—	77/3	—
Pulmonary artery	20/4	9	31/6	16	76/24	41
Pulmonary capillary wedge	—	7	—	—	—	0
Left atrium	—	—	—	4	—	0
Left ventricle	—	—	165/10	—	85/3	—
Brachial artery	118/64	80	169/90	113	95/48	63

component of the second sound. A clinical diagnosis of isolated congenital, pulmonic valvular insufficiency was made.

Catheterization of the right side of the heart with double-lumen Cournand catheter revealed normal pressures (Table I). During the latter part of diastole, the right ventricular and pulmonary arterial pressures were equilibrated (Fig 4). The cardiac output, measured by the Fick method and the vascular resistances were normal. Studies of blood oxygen, dye dilution curves, and hydrogen inhalation by means of platinum-tip electrode ruled out any intracardiac shunts. A selective biplane pulmonary arteriogram demonstrated regurgitation of contrast material from the pulmonary artery into the right ventricle with opacification of the entire right ventricular chamber. There was no evidence of stenosis involving the main pulmonary artery or its branches.

COMMENTS. It is interesting that the referring physician had made a diagnosis of pulmonic stenosis.

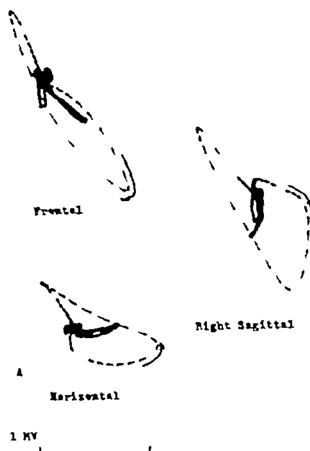


Fig. 2. Vectorcardiogram of Patient 1.

This is understandable, since the murmur had crescendo-decrescendo characteristic and was associated with thrill. Improper timing of the murmur could easily suggest the murmur to be due to pulmonic stenosis. As will be discussed later, the auscultatory and phonocardiographic findings in this case are typical of pulmonic valvular regurgitation. The only recommendation made to the referring physician was the use of prophylactic antibiotics.

Acquired. Acquired pulmonic valvular insufficiency is not common. Several causes have been reported, among which is tertiary syphilis,[27-34] which not only produces aneurysmal dilatation of the aorta but also affects the pulmonary artery in a similar fashion.[23,27,33,34] In one series of pathological cases of pulmonary arterial dilatations,[27] a luetic process was found to be responsible for 39 per cent of the cases. Syphilitic aneurysm of the pulmonary artery is usually associated with a similar process in the aorta but it may occur alone.[22] Syphilitic involvement of the pulmonary artery may cause varying degrees of cylindric fusiform or saccular dilatation of the main pulmonary artery or one of its branches.[27,31] Thrombosis is more commonly seen with luetic pulmonary arteritis than in luetic aortitis. Occlusion of branches of the pulmonary artery secondary to thrombosis with organization and fibrosis is not uncommon. The histopathological changes are similar to those which are usually associated with syphilitic aortitis.[27,34] In a classical review of the pathology of the pulmonary circulation by Brenner,[4] three patients with syphilis and pulmonary insufficiency murmurs were described. In one of these the cusps of the pulmonary valve were scarred and shrunken; in all



Fig 3 Roentgenogram of Patient 1

varying degrees of right ventricular hypertrophy were present

Other acquired forms of pulmonic valvular insufficiency include carcinoid and rheumatic heart disease[39,40] In both of these entities, other valves beside the pulmonic are involved Schwartz and Shelling[41] reported a case of rheumatic involvement of a congenital bicuspid pulmonic valve. Bacterial endocarditis may also cause pulmonary insufficiency[31,39,42] This is most frequently due to gonococcal infections.[44] Probably the most common form of acquired pulmonary insufficiency is that resulting from pulmonary valvotomy after surgery for congenital pulmonic stenosis.[43,44] Pulmonary insufficiency is almost invariably present in all cases and is well tolerated in the absence of any complicating factor[43] Rare forms of acquired pulmonary insufficiency reported in the literature include prolapse of the pulmonic valve through a ventricular septal defect[47] and as referred to by Kohout and Katz[46] trauma to the chest and infestation of the pulmonary artery by Echinococcus cyst.

The following case report presents an *example of an acquired form of pulmonary* valvular insufficiency and exemplifies the importance of the case history for an etiological diagnosis.

PATIENT 2 (QHC 00 58 60). A 56-year-old machinist was admitted on December 27 1964 to the Queens Hospital Center because of syncope which was felt to be due to a drug reaction. During the hospital stay a heart murmur was noted and further evaluation was requested The patient was known to have syphilis and had been deaf for two years. The deafness was felt to be due to syphilis.

On physical examination the pertinent findings were limited to the cardiovascular system. The blood pressure was 140/90 mm. Hg and the pulse rate was 54 per minute and regular There was no cyanosis or clubbing The peripheral pulses were equal and of normal quality The heart was not enlarged to palpation A diastolic thrill was

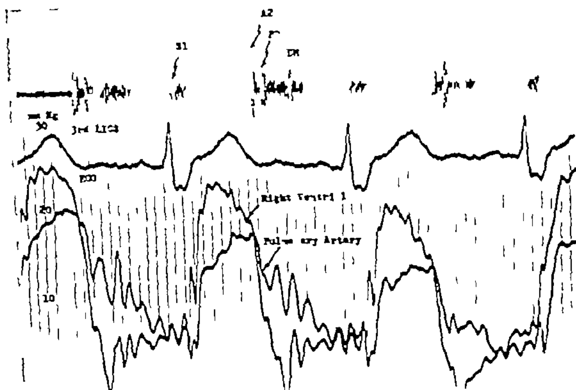


Fig. 4. Phonocardiogram and pulmonary artery and right ventricular pressure pulse. Note wide splitting of second sound and mid to late diastolic equilibration.

palpable over the second and third left intercostal spaces. The first heart sound was of normal quality. The second heart sound was neither split nor accentuated. A grade 2/6 systolic ejection murmur and harsh early to mid decrescendo diastolic murmur were heard over the second and third left intercostal spaces. Both the systolic and diastolic murmur increased in intensity on inspiration. There was no evidence of congestive heart failure. The remainder of the examination was within normal limits.

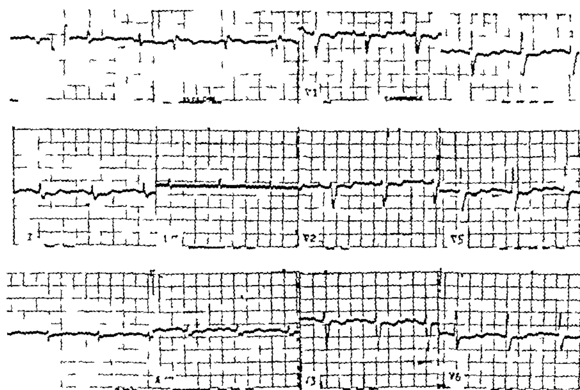
The serologic test (V D R L.) was strongly positive.

The electrocardiogram (Fig. 5) revealed normal sinus rhythm with slurred terminal S waves in Lead I and in all the precordial leads. The QRS duration was 0.10 seconds. The electrocardiogram was interpreted as nonspecific conduction disturbance. The vectorcardiogram (Fig. 6), made with the Frank lead system (tail leading), showed terminal conduction defect. The chest roentgenogram (Fig. 7) and cardiac series revealed heart of normal size with slight dilatation of the main pulmonary artery, diffuse tortuosity and some widening of the aortic arch. A phonocardiogram (Fig. 8) recorded at the second left intercostal space revealed an ejection systolic murmur and low frequency early-mid diastolic murmur.

Right and transeptal left heart catheterization was performed. The right ventricular end-diastolic and mean right atrial pressures were slightly elevated (Table 1). Late diastolic equilibration of the pulmonary artery and right ventricular pressures were noted (Fig. 9). The brachial arterial pressure pulse had no features of aortic insufficiency. Because of lack of cooperation on the part of the patient, further evaluation was not possible.

COMMENTS. According to the referring physician, who had known the patient for 15 years, murmur was first noted 8 years ago. The murmur in this case and the findings at cardiac catheterization, as discussed later, were characteristic of pulmonary valvular insufficiency. The patient was known to have had syphilis in the past and to have received a course of bismuth injections. He had never been treated with penicillin. Considering all the facts, one can infer that this patient had an acquired luetic form of isolated pulmonic valvular insufficiency.

Functional. Functional pulmonic regurgitation may be present in many instances of long-standing severe pulmonary arterial hypertension which may be either primary[4] or secondary to vascular changes due to mitral stenosis,[10-13] ventricular septal defect,[14] atrial septal defect,[15] or other con



ig. 3. Electrocardiogram of Patient 2.

genital defects associated with pulmonary hypertension. Pulmonary valvular insufficiency is not commented on in chronic lung disease associated with pulmonary hypertension.[36,38] Perhaps this is due to the emphysema which is usually present, which makes auscultation difficult.

Pulmonic valvular insufficiency may accompany an atrial septal defect even in the absence of pulmonary hypertension,[38] probably secondary to dilatation of the pulmonary artery. In one such case, the murmur persisted after operative closure of the atrial septal defect.

A diastolic blowing murmur at the base in the presence of mitral stenosis need not necessarily be a Graham Steell murmur, but may be due to aortic insufficiency, even in the absence of other clinical findings of aortic insufficiency. The presumptive diagnosis of a Graham Steell murmur requires clinical evidence of pulmonary hypertension.

The following case report presents an example of functional pulmonary valvular insufficiency secondary to pulmonary hypertension associated with an atrial septal defect and bidirectional shunting.

PATIENT 3 (QHC 05 88 41). A 39-year-old Negro housewife was admitted to Queens Hospital Center on May 4, 1966, for cardiac evaluation. When she was 23 yrs. old, the patient was first told that she had congenital heart disease, which was later proved at another hospital by cardiac catheterization to be an atrial septal defect. Recently the patient had had some mild exertional dyspnea and fatigue and was being treated with digitalis, diuretics, and a low-salt diet.

Physical examination revealed this woman in no distress. The positive findings were limited to the cardiovascular system. The blood pressure was 90/60 mm. Hg. The pulse rate was 86 per minute and regular. There was no apparent cyanosis or clubbing. The neck veins were flat. The point of maximum impulse was felt at the left fifth intercostal space and 3 cm. left of the midclavicular line. A prominent left upper parasternal lift was present. A diastolic thrill was felt along the left sternal border. The second sound over the pulmonic area was accentuated. An ejection click and a grade 2/6 ejection murmur was heard over the second and third left intercostal spaces. A loud, harsh, decrescendo murmur lasting throughout diastole, was heard over the left parasternal area. There was no evidence of hepatomegaly or peripheral edema.

The electrocardiogram (Fig. 10) and vectorcardiogram, (Fig. 11) revealed right ventricular hyper

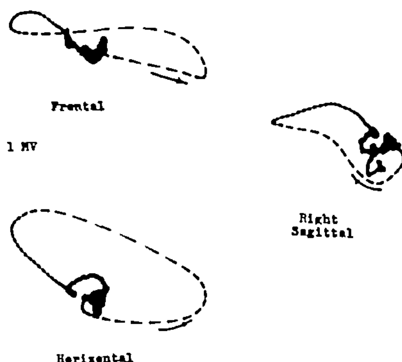


Fig. 6 Vectorcardiogram of Patient

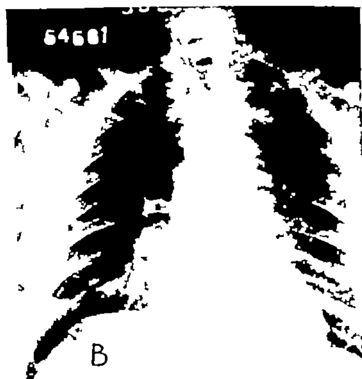


Fig. 7 Roentgenogram of Patient 2.

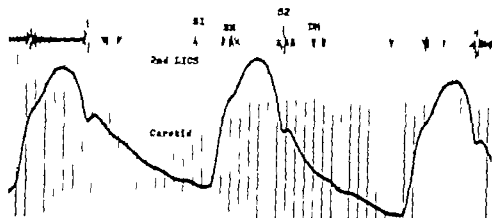


Fig. 13. Phonocardiogram of Patient 2 recorded over the pulmonic area.

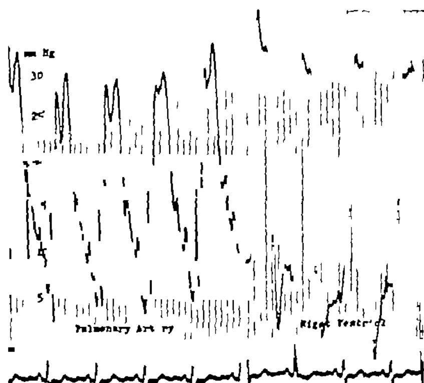


Fig. 14. Pulmonary artery and right ventricular pressure pulse. Note equal end-diastolic pressures.

trophy. The chest roentgenogram (Fig. 12) and cardiac series showed marked hilar vascular engorgement with cardiac enlargement characterized by prominence of the pulmonary artery segment and outflow tract of the right ventricle. The phonocardiogram (Fig. 13), as recorded over the third left intercostal space demonstrated an ejection click and a high amplitude second sound followed by a low-frequency murmur throughout diastole. The second heart sound revealed narrow splitting of its components.

Right heart catheterization revealed marked pulmonary hypertension (Table I). The pulmonary arterial pressure pulse (Fig. 14) showed a wide pulse pressure and a low dicrotic notch. The catheter was easily passed from the right atrium to the left atrium via an atrial septal defect. Studies of the blood oxygen, dye dilution curves, and hydrogen

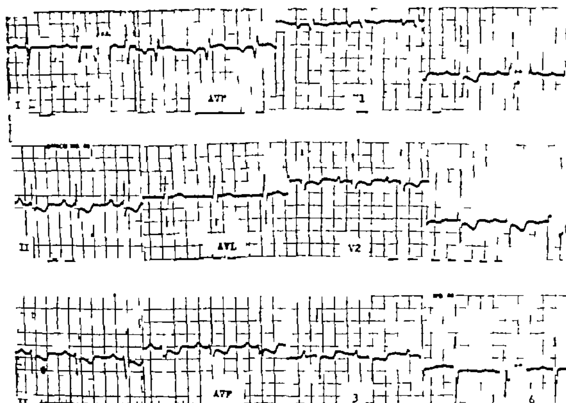


Fig. 10 Electrocardiogram of Patient 3

inhalation (with platinum tip catheter) revealed bidirectional shunting through an atrial septal defect.

COMMENTS. This case represents typical clinical features of pulmonary hypertension with the development of functional pulmonary valvular insufficiency. In the absence of a history of known congenital heart disease the differential diagnosis would include those elaborated above. Only by cardiac catheterization could a specific diagnosis be made. It is interesting to note that the son of this patient also has an atrial septal defect but no pulmonary valvular insufficiency.

Recognition

Auscultation and phonocardiogram. The murmur of isolated pulmonic valve insufficiency has characteristic features that allows one to make a clinical diagnosis at the bedside. In the first case a low frequency crescendo-decrescendo murmur was localized at the left second and third intercostal spaces during the first half of diastole (Fig 4). The murmur was accompanied by a diastolic thrill.

The distinct low frequency and crescendo-decrescendo characteristics of this murmur have been noted by others.[31,37,34,33] The murmur has a rough quality which may be confused with a friction rub or an extracardiac sound. The low frequency rough quality of the murmur is thought to be due to the relatively small diastolic gradient between the pulmonary artery and the right ventricle as compared to the high frequency blowing quality of aortic insufficiency which is accompanied by a large diastolic gradient between the aorta and the left ventricle.[34,38] By means of intracardiac phonocardiographic technique the diastolic murmur has been localized to the right ventricular outflow tract and the main pulmonary artery.[33,34] A rough low-pitch diastolic decrescendo murmur as occurred in the second case (Fig 8) has also been described in pulmonic valve insufficiency.[38,3] The localization and the quality of the murmurs are characteristic enough especially when accompanied by a diastolic thrill to allow one to make a diagnosis of pulmonary valve insufficiency. The diastolic thrill

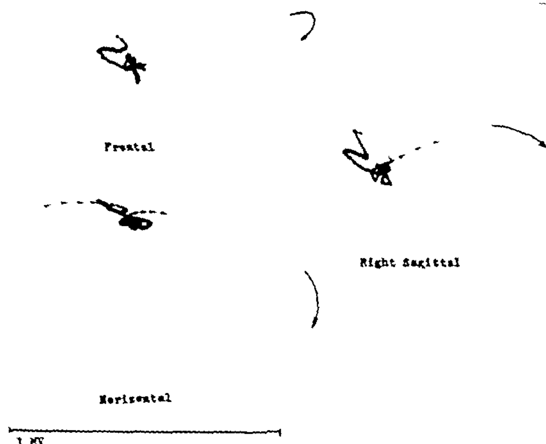


Fig. 11. Vectorcardiogram of Patient 3.

which was present in all cases is probably related to the close proximity of the right ventricular outflow tract to the anterior chest wall. The diastolic murmur may, as occurred in the second case, be accentuated by inspiration.[30] Amyl nitrate[40] and norepinephrine[1] have been reported to accentuate the murmur. A short low intensity ejection murmur over the pulmonic area is usually present and may be accompanied by an ejection click.[37]

The diastolic murmur of functional pulmonary insufficiency secondary to dilatation of the pulmonic valve ring as a result of pulmonary hypertension usually has a blowing quality similar to that found in aortic insufficiency. The third case presented is unusual because the murmur had a harsh quality (Fig. 13). In functional pulmonic insufficiency an ejection click is usually heard associated with a dilated pulmonary artery.

In order to distinguish between organic and functional pulmonary valve insufficiency, the characteristics of the second heart sound are of considerable importance. In the first two cases, the second sound was not accentuated. In the first case, where both components of the second sound were recorded, the aortic component had a greater amplitude then the pulmonic component. This feature would rule out pulmonary hypertension. In the third case, the second sound recorded over the third left intercostal space was very prominent, which would lead to the diagnosis of pulmonary hypertension. In organic pulmonary insufficiency, the second sound heard over the pulmonic area is usually not accentuated and may be inaudible, whereas in pulmonary hypertension accompanied by pulmonary insufficiency, the pulmonic component of the second sound is accentuated. Congenital absence of the

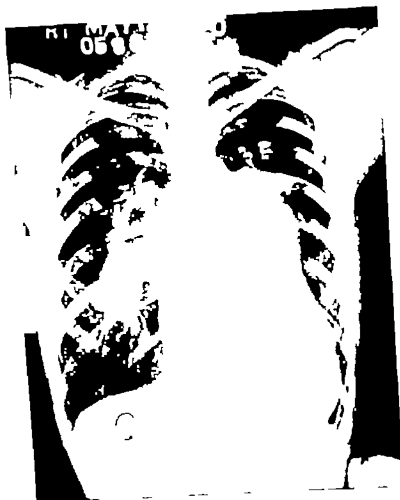


Fig 12 Roentgenogram of Patient 3.

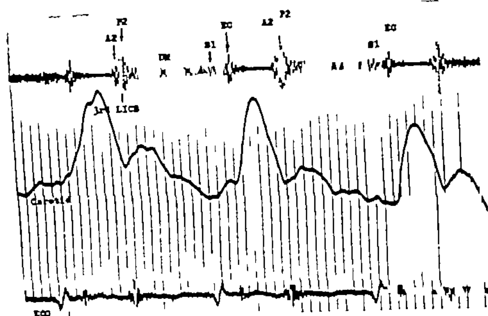


Fig 13 Phonocardiogram as recorded in Patient 3. Note prominence of pulmonic sound as compared to the aortic sound.

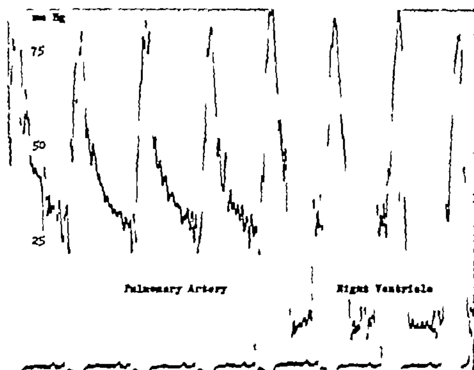


Fig. 14. Withdrawal pressure pulse from pulmonary artery to right ventricle in Patient 3.

pulmonary valve is usually suggested by a diminished or absent pulmonic component of the second sound.[7, 8-12] If one removes the pulmonic valves in dogs with resultant pulmonary insufficiency, a low frequency early diastolic crescendo-decrescendo murmur is obtained and the pulmonic closure sound can no longer be recorded.[12] It should be noted further that the diastolic murmur which accompanies idiopathic dilatation of the pulmonary artery is usually accompanied by an ejection click and wide splitting of the second sound with accentuation of the pulmonic component.[30,32] This can be distinguished from functional pulmonary insufficiency, since the two components of the second sound are narrowly split in pulmonary hypertension.[11,30] Jacoby and associates[11] commented further on the features of the second heart sound in pulmonary valvular insufficiency. They noted wide splitting of the second heart sound with only minimal variation during respiration and attributed this to diastolic overloading of the right ventricle and varying degrees of dilatation of the pulmonary artery. In the first patient of the present report, the second heart sound was split 0.04 to 0.05 seconds and varied little with respiration. This was suggestive of an atrial septal defect which was ruled out by cardiac catheterization.

Hemodynamics. Cardiac catheterization permits one to confirm the diagnosis of pulmonary valvular insufficiency and to rule out any associated factors. The systolic and diastolic pressures in the right ventricle are usually normal or may occasionally be slightly elevated. The cardiac output is normal or slightly diminished.[37] Of prime importance in making the diagnosis of pulmonary valvular insufficiency is the demonstration (Figs. 4 and 9) of mid or late diastolic equilibration of the pressures between the right ventricle and pulmonary artery.[4,11,37,4] There is usually an early diastolic dip in the right ventricular pressure with a resultant diastolic gradient between the pulmonary artery and right ventricle until equilibration of the pressure takes place. The early to mid diastolic gradient corresponds to the time when the diastolic murmur is heard.[4] The volume of blood that regurgitates during diastole is

felt to be related to this diastolic gradient as well as to the size of the opening of the regurgitant orifice.[3] The severity of experimentally produced pulmonic insufficiency in dogs depends upon the number of valve cusps removed as well as the level of the pulmonary arterial pressure.[22] This may explain why pulmonary regurgitation has led to severe right-sided heart failure when complicated by pulmonary hypertension[12,1] as well as in congenital complete absence of the pulmonic valve.[6,26]

The pulmonary arterial pressure pulse reveals a wide pulse pressure with a steep dicrotic limb and a low or absent dicrotic notch.[21,27] This pressure pulse contour found in pulmonary insufficiency should be distinguished from that seen in bilateral stenosis of the main pulmonary arterial branches, since the latter may be accompanied by a diastolic murmur, an increased pulse pressure, and a low dicrotic notch.[22] In this condition one finds an increase in the systolic pressure of the right ventricle and a gradient at the site of the branch stenosis. Neither of these was present in our cases.

In the patient with functional pulmonic valvular insufficiency there was no diastolic equilibration of the pulmonary artery and right ventricular pressures; however, the pulmonary pressure pulse revealed a wide pulse pressure and a low dicrotic notch similar to that seen in aortic insufficiency.

Another method used to demonstrate pulmonic regurgitation has been early detection of indocyanine green dye[44] or radioactive krypton[46] in the right ventricle after the injection into the pulmonary artery. Angiography has been utilized to confirm the diagnosis by demonstration of regurgitation of contrast material into the right ventricle after injection into the pulmonary artery by either biplane Schonander[43] or cineangiographic methods.

Management

The management of a patient with the murmur of pulmonic valvular insufficiency depends on the etiology and the presence of any associated lesions. All cases should be evaluated by cardiac catheterization. The authors have seen several patients who presented with only the murmur of pulmonic insufficiency and work up revealed tight mitral stenosis and severe pulmonary hypertension. One patient was followed as an example of primary pulmonary hypertension and on postmortem examination tight mitral stenosis was found with a small hypertrophied left atrium. The management of congenital pulmonic insufficiency depends on the presence of any associated lesions. Surgery for the associated anomaly may be indicated,[7,10,14] however, correction of the pulmonic insufficiency per se is not indicated. The only recommendation should be the use of prophylactic antibiotic therapy.[14,23] In acquired forms of pulmonic valvular insufficiency, the cause, if possible, should be treated (e.g., antibiotics for bacterial endocarditis and syphilis or drug therapy for carcinoid). Here again surgery for the correction of pulmonary insufficiency at the present state of knowledge is not indicated. In functional pulmonic valvular insufficiency, surgical correction for mitral stenosis, if it be present, should be performed. In the case of congenital heart disease complicated by pulmonary hypertension with functional pulmonary insufficiency, surgical correction of the congenital defect may be indicated if there is predominantly a left to right shunt; however, the surgical risk may be considerable.[14] Pulmonary valvular insufficiency secondary to bronchopulmonary disease requires the usual forms of therapy if heart failure is present. Attempts to relieve the anoxemia should be considered since this may be playing a role in the level of pulmonary hypertension present.

Summary

Three patients representing congenital, acquired, and functional pulmonary valvular insufficiency, respectively, are presented. The various etiologies of pulmonary valvular insufficiency are discussed.

During physical examination all patients demonstrated a distinct low-frequency diastolic murmur and thrill along the left sternal border. All three patients underwent cardiac catheterization studies. Mid or late diastolic equilibration of the pressures between the right ventricle and the pulmonary artery was demonstrated in the patients with congenital and ac

quired forms of pulmonic insufficiency. In the patient with functional pulmonary valvular insufficiency there were a wide pulse pressure and a low dicrotic notch. A discussion of the characteristic hemodynamic findings is presented.

It is concluded that this entity can easily be diagnosed by physical examination and confirmed by cardiac catheterization which may be supplemented by angiographic and dye dilution studies. Management depends on the etiology. Surgical correction is not indicated.

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The present status of clinical cardiac pacing

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Artificial cardiac pacing was first used clinically in 1952 for the relief of Stokes-Adams seizures due to ventricular asystole. This remains its major indication. New instruments, however, have increased the flexibility of the technique, particularly when employed in conjunction with pharmacologic agents.

Pacing modes

1. Fixed-rate asynchronous pacing. This mode, the most common in current use, is the standard treatment for ventricular asystole secondary to sinus arrest or, more commonly, to complete heart block. This is equally true whether the etiology of the arrhythmia is secondary to coronary artery disease, myocarditis, drug toxicity, or electrolyte imbalance. This mode stimulates the ventricles at a preset constant rate, regardless of the underlying cardiac rhythm or physiologic requirements, and eliminates the occurrence of Stokes-Adams seizures. It is safely and successfully applied in sinus bradycardia and in second and third degree heart block regardless of the atrial rhythm. The normal heart rate provided commonly suppresses the ventricular extrasystoles and abolishes the ventricular fibrillation that may occur as a complication of complete heart block with bradycardia. For patients who do not have Stokes-Adams seizures, but who may have cardiac, cerebral, or renal failure in the course of acute or chronic ventricular bradycardia, pacing at normal rates will increase the cardiac output to a degree consistent with the underlying disease. It may permit withdrawal of digitalis or diuretics, improve exercise tolerance, brighten the sensorium and, where function is marginal, relieve renal failure or cerebral confusion. In patients with congestive failure despite pacing, it permits free use of digitalis without fear of increased heart block and Stokes-Adams seizure.

Its value as a temporary measure has been well established in acute myocardial infarction or digitalis toxicity with transient heart block. It also has been used to sustain the ventricular rate during Pronestyl-induced ventricular depression, hyperkalemia, or propanolol intoxication with sinus bradycardia and acetylcholine-induced sinus arrest.

A major disadvantage of this system, particularly when it is employed as a permanent implant, is that a significant number of patients in whom pacing is initiated during symptomatic heart block subsequently return to conducted rhythms which conflict with the pacer stimulus. This is most common when the heart block is of recent origin, incomplete (second degree), or associated with shifting rhythms. In most instances this conflict causes no difficulty, particularly when the current applied is low. Occasionally, however, uncomfortable or disquieting ventricular arrhythmias develop and in rare instances, particularly during episodes of anoxia or electrolyte im-

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balance, induced ventricular tachycardia or fibrillation may occur In these cases, the use of digitalis to increase block, or the use of quinidine or Pronestyl to depress ventricular irritability do not always effect the desired result.

II Adjustable rate asynchronous pacing This is fixed-rate asynchronous pacing in which either the physician or the patient can vary the rate to meet specific needs. These may include changes in cardiac output for stress or rest, induced by higher or lower rates, respectively Occasionally rapid rates of 10 to 15 beats over the spontaneous rhythm ranging from 90 to over 140 beats per minute, are used to capture the heart and override multiple or multifocal prefibrillatory ventricular extrasystoles. With relief of ventricular irritability the rate is gradually returned to normal. When a null control is present it may be used to discontinue pacing in patients who return to suitable conducted rhythms. Although this type of pacing is available in totally or partially implantable units, it has its widest application in variable rate variable current, external pulse generators.

III Synchronous pacing Synchronous pacing is designed to stimulate the ventricle in response to an atrial signal received through a separate atrial sensing circuit. It is, therefore a variable rate pacemaker responsive within preset limits, to the normal physiologic variations of the sinus mechanism Because of atrioventricular synchrony it may provide a 10 to 20 per cent increase in cardiac output over that of asynchronous pacing at the same rate in the same individual and is optimally employed in the younger more active patient with heart block with a relatively intact myocardium in whom a maximal physiologic response is desirable. It may aid patients at the limit of their cardiac reserve in whom the atrial contribution may be the added factor that keeps them free of congestive failure Atrial synchrony is not a desirable system for patients who do not have stable atrial rhythms or who do have a poor myocardium intolerant of high normal sinus rates.

IV Standby or demand pacing This type of pacing is required to meet the needs of patients not in fixed block who nevertheless develop episodes of spontaneous or drug induced symptomatic bradycardia or asystole. These may arise during the course of sinus rhythm shifting A V block or any type of slow or rapid atrial or ventricular arrhythmia.

One pacemaker already available that functions to a large extent as a standby instrument is the synchronous system mentioned above. During normal sinus activity it operates as a mechanical A V conduction system with a short P R interval and paces the ventricle synchronously and continuously regardless of whether the underlying rhythm is stable or shifting between third second or first degree heart block sinus rhythm or ventricular asystole. Electronic blocking circuits prohibit the transmission of supraventricular tachycardia or flutter and keep the ventricular rate within preset physiologic limits. Sinus bradycardia or loss of the atrial stimulus precipitates fixed rate pacing at an automatic rate. Atrial fibrillation produces a variable ventricular response dependent upon the amount of voltage fed to the atrial sensor This ranges from atrial triggering at irregular occasionally rapid rates to fixed rate pacing Dominant ventricular rhythms may disrupt atrial synchrony capture the sinus trigger and throw a harmless and useless stimulus into the refractory phase of the spontaneous QRS Nodal rhythms may result in fixed rate pacing with competition. Some of the problems encountered with this pacemaker may be ameliorated by the adjunctive use of pharmacologic agents. Digitalis, particularly in atrial fibrillation may lower the atrial contraction voltage and slow or abolish atrial triggering Propanolol may be used to slow atrial tachycardias and Pronestyl to reduce ventricular irritability without fear of ventricular asystole. It may also be possible to slow the ventricular response of patients with a sinus rate near the upper limits of the pacemaker by slightly accelerating the sinus node by the use of atropine, to the point where every alternate atrial stimulus is blocked and the ventricular rate is halved

A variation of the synchronous circuit has been suggested as a second method of obtaining standby pacing In this, the sensor electrode is applied to the ventricle instead of the atrium and the sensor-stimu

lus interval is reduced to a few milliseconds. When spontaneous ventricular activity is present, at a rate or R-R interval above the preset automatic rate, the synchronized stimulus falls immediately into the completely refractory QRS of that beat and is ineffective. When the rate slows and the R-R interval lengthens to above the present value, fixed-rate pacing automatically supervenes. This system, therefore, is noncompetitive during normal or rapid rhythms of any variety and behaves as a fixed-rate pacer during the course of slow rhythms.

The third, more commonly employed method is basically a fixed-rate asynchronous pacer and controls slow ventricular rhythms exactly as does any fixed-rate mode. However, when spontaneous ventricular activity intrudes at a faster than the preset rate, a sensor feedback over the pacer electrode trips a blocking circuit that suspends the stimulus output until the ventricular rate returns to the preset R-R interval. No pacing artifact, therefore, is seen during normal sinus or nodal rhythms, atrial or ventricular tachycardias, extrasystoles, or any other rhythm with a ventricular response rapid enough to activate the blocking circuit.

In these last two systems, the use of pharmacologic agents does not modify the function of the pacer in any way except by precipitation of fixed-rate pacing in event of ventricular bradycardia. At the same time, both systems allow full play for the use of pharmacologic agents in normal or toxic doses for control of atrial or ventricular arrhythmias while safeguarding against the development of ventricular bradycardia or asystole.

I. Coupled or paired pacing. This technique is, for the most part, a research tool. It occasionally is used clinically to slow symptomatic atrial or ventricular tachycardia, particularly in patients refractory to more conventional methods (drugs or cardioversion). Its action is effected by the introduction of a pacing pulse just at the end of the refractory period of either a spontaneous (coupled) or previously stimulated (paired) beat. This second pulse does not produce a contraction, but it does result in an electrical depolarization which increases the refractory time of the effective beat and which may result in slowing of the heart to nearly one half of the primary stimulus rate.

Instrumentation and methods of application

Several types of pacemakers of United States manufacture are now generally available. These include many models designed for fixed or adjustable rate pacing and one for synchronous pacing. Power sources, at present, are limited to house-supplied alternating current for bedside systems, standard or nickel-cadmium rechargeable batteries for portable units, or mercury cells for personally carried exteriorized or implanted pulse generators. The stimulus is transmitted by externally placed transcutaneous electrodes or by exteriorized implanted direct myocardial or transvenous endocardial electrodes. There have been no major alterations in design or application of these instruments in the past 2 or 3 years. A review of the available and immediately projected equipment, however, is warranted, particularly as it relates to newer, more flexible usage or special problems encountered.

I. External stimulation

EXTERNAL TRANSCUTANEOUS PACEMAKERS. These are immediately applicable to the closed chest, and require little training to use. They supply 2 millisecond pulses of 50 to 150 volts at adjustable rates and are now manufactured by almost all of the companies supplying pacemakers or intensive care and monitoring equipment. Most are A.C. powered, but at least 4 companies* have battery-powered portable units. Many embody an asystolic alarm feature that may be adjusted to trigger fixed-rate pacing following a preset interval of absent R or S waves. This feature is not "fail safe" when used with patients already on a pacemaker but under observation for possible malfunction, as a high voltage pacemaker artifact (whether or not followed by a myocardial contraction) may be interpreted as an R or S signal. An alarm response and frequently an adequate paced response may be elicited, however, if the chest elec

*Electrodyne Co., Inc., Norwood, Mass.; Medtronic, Inc., Minneapolis, Minn.; Travenol Laboratories, Morton Grove, Ill.; General Electric Co., Milwaukee, Wis.

trodes are repositioned to reduce the monitored amplitude of the pacemaker artifact and/or enhance that of the real R or S wave so that sensor circuit differentiation of their apparent voltage is possible. Demand or standby control of pacing may be available through at least two companies.* Pain, galvanic spasm, and possible skin burns remain limiting factors in the prolonged use of this method.

II. External percutaneous pacemakers. Emergency pacing of the ventricles now is effected commonly by percutaneous transvenous right ventricular endocardial stimulation through catheter electrodes.

Three types of percutaneous electrodes are now available: (*a*) Semi-firm. These are similar to diagnostic cardiac catheters in construction and handling and are positioned under fluoroscopic control. The major manufacturer, United States Catheter and Instrument Corp. (USCI),† uses a woven Dacron radiopaque plastic-coated sheath over a braided steel wire core. The Electro-Catheter Corp.‡ has single strands of copper sheathed in Corolan. Both companies use platinum intracardiac terminals and make a variety of unipolar, bipolar, and multipolar units in several French sizes. (*b*) Soft and flexible. These are limp, difficult to manipulate, and may require guides for positioning. One (Medtronic, Inc.) consists of a steel coil spring Silastic-sheathed platinum-tipped unipolar or bipolar electrode with a bulbous end of 10 Fr. and a 6 or 7 Fr. shaft. This is positioned under fluoroscopic control with the help of straight or gently curved steel wire stylli temporarily inserted through the coil spring core. (*c*) Floatation. This is a light, limp unipolar platinum-tipped Teflon-sheathed braided steel electrode.§ It is floated into the heart through a 17T needle or a suitably sized venatube under electrocardiographic, rather than radiographic, control.

The safest route of percutaneous application is still via the right or left external or internal jugular vein. The catheter is subject to almost no stretch dislocation or angulation by motion of the head, arms, or shoulders. The path is short, almost entirely intrathoracic, and motion stress is minimal. The semi-firm catheters are positioned in the mid-outflow tract and secured by two sutures of 2-0 braided steel wire buried within the incision if prolonged use is anticipated or applied to the skin near the exit sinus if brief application is planned. Fabric or plastic sutures do not secure the smooth, firm surfaces of these catheters with a sufficient grip to prevent slipping with an active patient. The flexible catheters will not stay in the outflow tract and must be positioned in the apex of the right ventricle and secured by plastic sutures. Silk sutures may lose their grip even with these soft catheters and wire sutures will cut the insulation. With both types excess internal length of catheter may cause angulation with displacement or excess pressure on the myocardium. Insufficient length of catheter will lead to withdrawal from endocardial contact on deep inspiration. Fluoroscopic observation in the anteroposterior and left lateral positions during exaggerated respiration, coughing, or Valsalva maneuver before final suturing will confirm the anatomic stability of the installation. Electrical threshold must also be checked out at this time. Unless it is below 1.0 Ma. (USCI) or 2.5 Ma (Medtronic, Inc.), placement is definitely suboptimal and repositioning may be in order. USCI bipolar electrodes, applied by this technique with buried sutures, have remained in situ for 3 to 4 years without displacement, internal breakage, or significant infection. Postmortem inspections of the USCI catheters have shown no overt deterioration of sheath or platinum electrode and little tendency to endothelial sheathing or clot attraction. Silastic or polyethylene-sheathed electrodes should not be applied in this manner except for short periods, as it is now clearly established that within weeks to months variable amounts of endothelization occur that may fix the catheter to the walls of the heart or great veins. This, potentially, could make late withdrawal difficult, perhaps impossible, in catheters with bulbous tips.

The brachial vein route, though commonly used, is unsafe unless final positioning is done with the arm down at the pa

*American Optical Co., Chelsea, Mass.; Electrodyne Co., Inc., Norwood, Mass.
†Glens Falls, N. Y.
‡Linden, N. J.
§Davis and Geck Div., American Cyanamid Co., Pearl River, N. Y.

tient's side and then immobilized by strapping to the chest. When the arm is free, elevation lengthens the venous path, pulling the catheter fixed at the elbow out of position and lowering shortens the tract thrusting the catheter forward. This may disrupt pacing and lead to gross malpositioning or even myocardial perforation whether the catheter is positioned in the outflow or apex of the ventricle.

The fastest percutaneous emergency approach is passage of a USCI or Elecath electrode through a large-bore Teflon needle from the femoral vein to the apex of the right ventricle. Patients with this installation should not be allowed to ambulate but may be given limited chair privileges with injunction against flexion of the leg at the hip of over 45 degrees to avoid forward thrust of the electrode seen with acute angulation. This mode is rarely used for more than 7 to 10 days, as there is a heightened tendency for clot formation in the inferior vena cava as opposed to the superior vena cava with long-term application. It is excellent for short periods before permanent installation or during repairs or battery replacements as it is virtually atraumatic and does not sacrifice a vein.

The Davis and Geck electrode may be applied from the brachial, external jugular, or subclavian vein. It has the advantage of bedside application and requires no specialized training other than knowledge of the intracardiac electrocardiogram. It is not always, however, as certain and rapid a method as direct visual placement and may, if it floats free, need higher currents to pace the heart. It has been used safely and satisfactorily for weeks of pacing.

Any pulse generator can be applied to these electrodes, including the internal mode of bedside A.C. instruments, if they are properly grounded and not used in conjunction with other electronic equipment that may set up current loops. Isolated battery-powered generators are much safer. Portable transistorized battery packs that make ambulation possible are available for fixed rate pacing (Medtronic, Electrodyne) and are in clinical research for demand modes (Cordis Corp., American Optical Co., and Medtronic Inc.). Paired pacing (Medtronic) is too critical a procedure to be considered as an ambulatory method. Bipolar electrodes are applied with the distal pole to the negative and proximal pole to the positive terminal of the pulse generator for all of these generators. Unipolar electrodes are applied to the negative pole and a plastic-insulated wire suture in the subcutaneous tissue completes the circuit to the positive pole.

Percutaneous myocardial wires applied during surgery for temporary postoperative pacing also may be used in the circuit suppression or ventricular synchronous standby, demand, or paired and coupled modes.

The use of emergency myocardial electrodes applied by transthoracic needles (Elecath) is risky for any mode, but cannot be excluded from consideration when other methods are unavailable.

During closed chest massage the use of sensor circuits is questionable as artifact signals may be produced causing pacemaker malfunction.

III. Implantable pacemakers. Two types of fully implantable pacemakers are now in clinical use. Most common are the fixed rate asynchronous units with myocardial wire electrodes applied by thoracotomy or more recently, with transvenous endocardial catheter electrodes.[4] Pulse generators for these instruments have been commercially supplied in the United States for several years by the Medtronic, Inc., Electrodyne Co., Inc., General Electric Co., and Cordis Corporation. Their Mallory mercury batteries are not guaranteed beyond 3 years and Medtronic and Cordis suggest obligatory replacement in 2½ and 3 years. Some units fail to reach this point. Battery decline is commonly signalled by a rate change. Element failure, particularly of timer circuits, has diminished with protective redesign against the 100 per cent humidification that ultimately penetrates the imbedding compounds. Medtronic, Cordis, and Electrodyne still use a current pulse of approximately 2 milliseconds and General Electric of 2.5 to 3.0 milliseconds, in spite of the fact that it has been demonstrated that battery life might be spared by limiting the pulse length to 1 millisecond without significantly altering the current

Escher Longdwell Teflon Needle—Becton, Dickinson and Company, Rutherford, N. J.

requirements. The current outputs of these units are 0 to 9, 8 to 9, 10 to 14, and 5 to 9 Ma. respectively. High output units are made for patients with impedance problems. Most pulse generators are preset at 70 ± 2 beats per minute, but may be ordered for other rates. Adjustable rate controls are available in models of Medtronic (Keith needles) and General Electric manufacture. The latter may be externally adjusted by a dual rate magnetic switch (64 and 82 beats per minute) or a radio transmission coil which varies the rate from 70 to 120 beats per minute but halves the power output at the top rates.

All of the myocardial electrodes have undergone reinforcement or redesign to diminish the incidence of wire fracture and to facilitate pulse generator replacement. Cordis has changed from a platinum iridium to an Elgiloy coil spring core. General Electric from a steel wire braid to a steel coil spring core. All have separable plug in attachment.

The Medtronic bipolar transvenous implantable electrode is similar to the percutaneous catheter and may be applied through the external or internal jugular vein or the cephalic veins, with the same criteria for positioning and threshold. The Cordis electrode is a unipolar Elgiloy coil spring catheter with a 4 mm. platinum tip and a threshold of under 1.0 to 1.2 Ma. The threshold of both of the electrodes positioned at the apex, may increase by 3 to 5 times during the first few weeks or months of use. This makes it important that they have minimum threshold at implantation, as the increase may exceed the pulse generator output in some assemblies. This is in opposition to the USCI electrode positioned in the outflow tract where significant increase in threshold is rarely observed even after years of use. Both of the Silastic sheathed electrodes may fix into place by endothelization. They have the same stability as the percutaneous electrodes in their intracardiac course but are subject, as are the myocardial electrodes, to fracture in their extracardiac course. The major stress is elevation of the arm on the implanted side from 90 to 180 degrees. Fluoroscopy of these electrodes, and also of myocardial implants, during body motion will sometimes permit prediction of or establish the reason for breaks based on fulcrum formation.

The second fully implantable type is the Cordis synchronous pacemaker. Its ventricular pacing components are the same as those of the fixed-rate units. The atrial sensor requires 1 mv. of current from an atrial myocardial Elgiloy wire for activation. The transvenous assembly, not yet released from clinical trial, requires 0.5 mv. obtained through a second Elgiloy coilspring catheter hooked high into the right atrium.

None of the demand pacemakers (Cordis, American Optical, and Medtronic) have been released from clinical trial.† The major deterrent with these instruments is that their ventricular sensor circuits may be activated by adventitious high voltage currents. This has also been noted on rare occasions with the atrial sensors. In the synchronous units, Cordis atrial or ventricular, this does not stop pacing but drives the rate up to its maximal limit of 120 to 140 beats per minute. In the circuit blocking units, pacing may become irregular or stop. Shielding of the pulse generator is only a partial answer, as the electrode remains exposed. The tremendous usefulness of these modes, however, warrants intensive consideration.

Paired and coupled pacing are available, at present, only through Medtronic, Inc.

A partially implantable asynchronous radiofrequency pacemaker is also in clinical trial as a myocardial or transvenous instrument. This is a completely redesigned version of the Glenn-Mauro-Eisenberg pacemaker. The transvenous electrode is a USCI catheter. The receiving coil and electrode are fully implanted, while the pulse generator and broadcasting antenna are exteriorized. This permits rate, current, and battery changes or discontinuation of pacing, as in an exteriorized unit, but excludes the possibility of infection from an open sinus. Long term care of the antenna and carrying of the pulse generator are the price of this flexibility.

It is obvious that the major clinical change in the last several years is that implanted pacemakers need no longer be

*Airborne Instrument Laboratories, Deer Park, Long Island, N. Y.

†By the time of publication, one or more of these companies may be releasing demand pacemakers for general use.

applied by thoracotomy Paired pacing demand and standby pacing and full integration of pharmacologic and electrical therapy regrettably are still limited largely to experimental laboratories Research has not yet produced a proved alternate to periodic surgery for battery replacement. Externally rechargeable batteries body fuel cells and atomic power are still in exploration Component reliability and miniaturization progress slowly Elimination of electrodes by implantation directly in the heart requires a return to thoracotomy No other feasible alternative has yet been developed The application of emergency pacing at the bedside has been facilitated by introduction of the Kimball Killip technique and may be improved by clinical application of current research in magnetic guidance of similar light electrodes. European research offers no additional break through

The flexibility of the standby or demand units particularly when used in conjunction with pharmacologic agents, clearly extends the therapeutic usefulness of pacing and warrants their introduction although their stability and safety must be evaluated further

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Annotations

Analgesic nephropathy in Australia

Renal papillary necrosis has long been known to occur in diabetes, and in obstructive uropathy when infection is present. In recent years, many reports, mainly of retrospective investigations, have shown that cases of bilateral generalized papillary necrosis, usually accompanied by considerable renal contracture and terminally, at least, by renal infection, have followed excessive ingestion of analgesic mixtures containing phenacetin. Evidence of impaired renal function has been found in a high proportion of patients consuming large amounts of analgesics, the risk rising with the amount of analgesic consumed.[4] A recent annotation in this JOURNAL discussed the contribution which aspirin might make to this form of nephropathy and concluded that it was not an essential factor and, possibly not a factor at all. The main suspicion continues to fall upon phenacetin or its associated impurities.

The type of nephropathy linked with excessive use of phenacetin has varied in its incidence from country to country. Originally described in Switzerland, it was soon found to be especially prevalent in Scandinavian countries. By 1961 in Sweden, the evidence implicating phenacetin was considered to be strong enough to warrant banning the sale of analgesics containing this drug to the public except upon a doctor's prescription. In Australia, in 1962, there were indications that analgesic nephropathy was common. Jacobs and Morris[8] found 50 cases of papillary necrosis in 1,350 autopsies in Sydney, New South Wales, and established a history of excessive use of analgesics in 47 of these cases. Workers in Melbourne, Victoria, and in Queensland were also familiar with the disease.

Two recent reports suggest that, in Australia, analgesic nephropathy is becoming a major public health problem. A prospective autopsy investigation carried out in Brisbane, Queensland, correlated renal findings with analgesic consumption. A pathologist examined all kidneys from the 507 autopsies performed through 1964, and graded the changes in the renal pyramid as papillary necrosis, necrotizing papillitis, and necrobiosis, in descending order of severity. The collaborators were able to obtain information on the consumption of analgesics from relatives of the deceased in 437 cases. The two sets of data were obtained independently. It was found that no fewer than 69 of the patients had taken more than 2 kg of phenacetin during life. Of these 69, 20 had papillary necrosis, 19 had necrotizing papillitis, 10 had necrobiosis, and 3 had advanced bilateral phosphatic calculous disease, possibly superimposed upon papillary necrosis. In only 17 cases were no notable papillary abnormalities found. In the 388 patients who consumed less than 2 kg of phenacetin, generalized papillary necrosis, or necrotizing papillitis, was found in only 3 cases in the absence of obstruction or diabetes. The degree of papillary damage in patients taking more than 2 Kg of phenacetin correlated broadly with the total amount of phenacetin consumed. Severe damage was rarely seen in less than 5 years, and only 1 of the 19 deaths from analgesic nephropathy occurred in less than 10 years. In view of the fact that 75 per cent of the patients taking more than 2 kg of phenacetin showed papillary changes, it may be significant that no papillary abnormalities could be found in any of a small group of 6 patients who had taken over 2 kg of aspirin in preparations not containing phenacetin. The Brisbane investigation showed clearly that papillary changes precede the development of histologic or bacteriologic pyelonephritis. The second report,[10] from Melbourne, based on both clinical and pathologic findings, confirmed this important observation. The Melbourne workers saw almost 100 patients with papillary necrosis in 4 years. Over a third of these patients never showed evidence of renal infection, and the urine was repeatedly sterile. Two of these patients at autopsy showed no evidence of active pyelonephritis. However both the Brisbane and the Melbourne groups found that the majority of their patients who died from analgesic nephropathy did show evidence of pyelonephritis at the time of death. It is probable, therefore, that, in Australia at the present time, most deaths from analgesic nephropathy are certified as being due to pyelonephritis.

In an analysis of the over-all pattern of renal disease in Queensland based upon the 1964 autopsy series, it was shown that analgesic nephropathy was by far the most important cause of renal failure, outnumbering pyelonephritis of other types two to one. On the basis of these findings, it was suggested that the threefold increase in the death rate for pyelonephritis in Queensland recorded by the Commonwealth Statistician since 1955 could be due largely to the emergence of analgesic nephropathy. Similar rises in mortality rates have also occurred in Victoria and in New South Wales (the state lying between Victoria and Queensland) in both sexes, although the increase has been more striking in females. An interesting difference in rates was noted. In 1964 the death rate for pyelonephritis in Queensland was three times as high as that in Victoria, whereas the rate in New South Wales was

twice that in Victoria. Queensland, lying partly within the tropics, has a much hotter climate than Victoria, and it was suggested that the elaboration of more concentrated urine could accentuate the presumed nephrotoxic action of phenacetin. The alternative possibility that the Queensland population consumes greater quantities of analgesics cannot be excluded because, although there is evidence that the current consumption of analgesics in Queensland is very high, no comparable information is available from Victoria.

To date, it would appear from the paucity of reported cases that analgesic nephropathy is not an important problem in the United States. If it can be shown that the consumption of analgesics over the past 10 years is comparable with that in Australia, whereas large prospective autopsy surveys fail to show significant numbers of cases with the changes of analgesic nephropathy, it will be possible to conclude that there is some element in the Australian environment or in Australian analgesics that is peculiarly inimical to the kidney.

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Practical and training aspects of teaching ventilatory resuscitation

Today there is no doubt about the superior effect of mouth-to-mouth or mouth-to-nose breathing compared with the chest-compression methods. Nevertheless, various rescue organizations persist in teaching one or more of the chest-compression methods and some organizations recommend them as being more effective than direct insufflation of the lungs by mouth!

But these organizations do not consider that in the teaching of ventilatory resuscitation to laymen and paramedical personnel two problems are of practical and pedagogical importance: (1) the possible differences between the resuscitative methods in physical load on the rescuer if performed for a long period of time, and (2) adoption and memory of the different methods after a certain lapse of time. Therefore we decided to choose mouth-to-mouth, mouth-to-nose, Holger Nielsen, Silvester, and Thomsen rescue breathing for a trial. Two or more of these methods are still being taught during the training program of rescue organizations in Germany. Volunteer soldiers, 19 to 23 years of age who had never received any training in resuscitation underwent the trial. Ten volunteers were taught the 5 resuscitative methods. For the exhaled-air methods the Ambu-phantom was used, whereas the 3 manual methods were performed on other volunteers. Training for the manual methods lasted three times as long as did that for the exhaled-air methods. To determine the differences between the various methods in regard to the *physical load* borne by the rescuer, it was believed it sufficient to measure pulse frequency, blood pressure, loss of weight, and increase in body temperature during the 1-hour period that rescue breathing was performed.

The sequence according to which the volunteers

performed the various methods was planned by means of the latin square in order to avoid spreading factors which influence statistical significance. Every 10 minutes, pulse rate and blood pressure were measured. At the end of 1 hour of ventilation, body weight and body temperature were compared with the values obtained prior to the trial.

The evaluation performed by pluralized variant analyses separated for pulse rate, blood pressure, loss of weight and body temperature showed according to the Friedmann test, by all criteria no significant differences between the mouth-to-mouth and mouth to-nose methods or between the 3 chest compression methods. Combining the mouth-to-mouth and the mouth-to-nose methods int one group, and the 3 chest-compression methods into second group, significant differences could be measured statistically. A much greater physical load is put on the rescuer when he is performing one of the chest-compression methods than one of the exhaled-air methods.

Furthermore we tried to discover the differences which probably exist between the 5 above-mentioned methods according to the *adoption and memory* of the volunteers after certain lapse of time after training. It seems to be important to know which of the methods would be chosen by the rescuer in the event of sudden catastrophe. Twenty-seven volunteers were trained with the same instruction equipment. Most of the training consisted of practical exercises combined with current correction of possible mistakes. After 5 months, the 27 volunteers were tested. They did not have prior knowledge of either the date or the nature of the test. One by one they were called into separate room, and each, without hesitation, had to tell which method he would prefer. Beside the method of choice he had to perform all of the other methods that he had learned.

Some of the most important criteria for evaluation were free air-passage, sufficient breathing, and correct chest pressure. No significant differences between the mouth-to-mouth and mouth-to-nose methods or between the chest-compression methods were found by the Friedmann test. We combined the 5 methods into two groups as described above. The superior value of the exhaled-air methods was proved subjectively and objectively. With the direct methods 92.6 per cent of the operators were classed as correct, and 7.4 per cent as satisfactory. With the manual methods 19.8 per cent were correct, 44.4 per cent were satisfactory, and 35.8 per cent were unsatisfactory. There were almost eighteen times as many mistakes with the manual methods as with the direct methods.

It may be said that, besides the physiologic effects the chest-compression methods for ventilatory resuscitation do not prove to be satisfactory in regard to physical load or adoption and memory in the training of laymen. It was found that the exhaled-air methods are very much superior to all other methods of artificial ventilation. It would seem that the training of laymen, and probably also of paramedical personnel, in chest-compression methods is doubtful procedure and a waste of time.

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Heterograft aortic valves for human valve disease

Twenty-one heterograft aortic valve replacements have been performed over the last one year at St. Vincent Hospital, Melbourne. Heterografts have advantages over other implantable valves, and the reasons for our preference will be discussed after presentation of our clinical experience.

A large valve bank of some 50 pig and calf valves has been readily established. Fresh valves have been collected under nonsterile conditions. Preservation and sterilization has been with buffered acid formaldehyde solution. The aortic sinuses of each heterograft are tightly packed with wool soaked in the preservative in order to maintain the cusps and annulus in the natural shape. After several weeks, the valve is trimmed of all ventricular muscle, leaving a very strong but thin, rim of annulus and aortic wall. Particular care is taken to measure the valve accurately and at each operation 4 to 5 heterografts of varying sizes are made available. The unused valves are returned to their individual jars containing the formaldehyde. They can and have been inserted at subsequent operations. Careful measurement of the host aortic annulus is performed and a slightly larger heterograft is inserted. The aim of this technique[1] has been to ensure a competent valve. A single continuous suture, passing the needle very deeply through both host annulus and heterograft rim has given a satisfactory firm implantation. Interrupted or additional sutures have been used in segments of the host rim that have been extensively decalcified.

Our experiences with the calf and pig valves are expressed in Table I. Of the 21 patients, 9 have required double-valve surgery with replacement of both the aortic and mitral valves in 7 patients. Nineteen patients in this initial series left hospital. The 2 deaths were unrelated to the heterograft valve function. The one late death at 2 months was due to

Table I. Results of heterograft replacement, total number, type of heterograft and operation, and mortality figures

Number	Operation	Mortality	
		Hospital	*Late*
21 (15 calf and 6 pig)			
7	Aortic heterografts + Starr mitral prothesis	0	1 (2 mo.)
2	Aortic heterograft + mitral annuloplasty Aortic heterograft + mitral valvotomy	0	0
12	Aortic heterograft	2 (second and eleventh days)	0

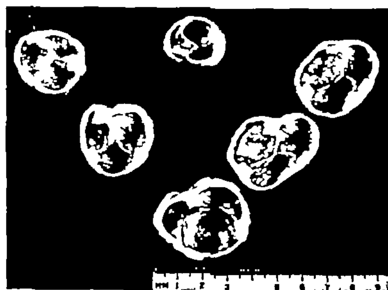


Fig. 1. Pig and calf heterograft aortic valves are available in a variety of sizes. The valves shown here have been trimmed fully and are ready for implantation.

infective emboli from the mitral valve prosthesis, which was covered with thrombus. The heterograft was absolutely clean and histologically well incorporated at the suture line with the host tissue.

The most encouraging features have been the correction of the hemodynamics and the absence of the need to use anticoagulants in patients with the single heterograft aortic replacement. On careful clinical examination, only one patient has a soft aortic diastolic murmur. This has diminished in intensity; there are no peripheral arterial signs of incompetence, and the cuff blood pressure was last recorded at 120/85 mm. Hg.

Three patients have been restudied by cine-aortography. A wide-open valve orifice is visible during ventricular ejection. Competence is present in 2 patients, and a "puff" of regurgitation (less than minimal, undetectable clinically) is seen in the third. All of the surviving patients have improved in exercise tolerance and they have returned to work or to home duties at the anticipated time intervals postoperatively.

The follow-up is still short and, although we are encouraged by the function of the heterografts, we consider that such operations should be recommended only to patients with severe symptomatic disease.

Heterografts would appear already to have some

advantages over other valves. Prosthetic valves have the postoperative complications of thromboemboli, of anticoagulants, of infection, and of structural changes in the prosthesis itself Homografts, although free of thromboemboli, are not so readily obtainable in such wide range of sizes, and significant clinical residual or postoperative aortic incompetence does occur in proportions sufficient to make one doubtful about their universal use. Since heterografts are vailable in all sizes (Fig. 1), the difficulties of matching and of implanting competent valve are not so great. I addition, the supply of heterografts is unlimited. Fifteen to twenty valves are obtainable within one-half hour t each visit t our abattoirs.

W have found that the animal valves are most desirable, firstly for young patients, particularly women of the child-bearing age and secondly for those from country centers where control of anticoagulation has already proved to be difficult and hazardous in patients with prosthetic valves.

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Mechanical hemolysis in patients with valvular heart disease and valve prosthesis

Postoperative hemolytic anemia in patients with intracardiac prosthetic devices, although rare despite the increasing use of well-tolerated synthetic materials, is another complication of open-heart surgery Besides experimentally induced hemolysis in laboratory animals,[34] the first published and still one of the clearest accounts of this anemia in man is that of Sayed and associates.[18] After large septum primum defect had been repaired with Teflon graft, this patient developed intravascular hemolysis with continuous hemoglobinuria. The ppearance of distorted and fragmented red cells supported the hypothesis that regurgitant jet of blood from cleft in the mitral valv was playing on the Teflon septum and was thereby undergoing a significant amount of traumatic hemolysis. Hemolysis ceased immediately when sandpaper-like cul-de-sac at the base of the bare Teflon was covered up.

Our first observations of the sudden development of hemolytic anemia in 2 patients who had had Hufnagel tricuspid Dacron prosthesis inserted because of aortic insufficiency strongly support the hypothesis that this type of hemolytic anemia is of mechanical origin. The fact that intravascular hemolysis with hemoglobinuria took place simultaneously with the loosening of two sutures seems to indicate that red blood cells are mechanically fragmented by unusual intracardiac turbulence and probably by regurgitant jet of blood acting upon the uncovered suture part of the Hufnagel prosthesis. The occurrence of fragmented red cells (burr cells, helmet cells, schistocytes, fragmentocytes, pyknocytes), first described by Ehrlich, in 1891 and lready considered by Rindfleisch to result from mechanical factors acting on red cells, favors the concept of mechanical hemolysis. Furthermore, the same type of red cell is well known in other conditions of presumably traumatic origin (microangiopathic hemolytic anemia, march hemoglobinuria). I the patient with hemolytic anemia after open-heart surgery schistocytes are, nevertheless, only a small portion of the total circulating red blood cells even though cross-survival time studies have show that the abnormality is due to an extracellular defect rather than to an intracellular defect.[6,11,14] Studies using differential centrif gation may explain the nonuniform degree of schistocytosis in these patients by cell aging being prerequisite for the formation of schistocytes.[19] Despite the correlation between the number of schistocytes and the degree of hemolysis in larger series of patients with artificial heart valves, survival studies suggest that the circulating schistocyte is not irreversibly damaged since the patient red blood cells survive normally when transfused into normal recipients [12,13] Nevertheless, hemolysis seems to be due to repeated mechanical trauma to aged red cells in the affected patient, with constant fragmentation inducing final hemolysis of these red cell fragments hemolysis being either severe or compensated.[20]

Despite the severe morphologic changes, an enzymatic or immunologic basis was excluded in all patients studied so far. Only the group at the U iversity of Oregon[4,20] has found a weak positive antiglobulin test in some of their patients, which suggests modification of the red blood cell surface antigenic

tat by the turbulent blood flow I our series and in all others the repeatedly performed antiglobulin test was alw y negative and steroid therapy proved to be ineffective and tests for paroxysmal noc turnal hemoglobinuria were negative, as well.

Exactly why hemolysis takes place in these pa tients remains unknown E ery example of this type of anemia showed evidence of persisting hemodynamic defect in the case of alvular prosthesis t was mainly residual aortic regurgitation owing to a leakage of blood around the sutured alve But in estigations in our laboratory using red cell sur vi l studies indicat that t least compensated hemolysis has high frequency (64 per cent) in patients with different types of h la prosthesis which suggests that regurgitation is not the only factor inducing hemolysis It also seems t be quit clea that the transvalvular pressure gradient is not the only precipitating factor since in our series severe hemolytic anemia occurred in patients with a Starr Edwards prosthesis and postoperative pressure gradient of only 10 mm Hg and hemolysis was even demonstrated in patients w th mitral Starr Edwards prosthesis but not in patients with isthmus stenosis.[14] Preliminary experimental studies in our laboratory seem t suggest that extreme intracardiac t rbulence around the nonlongitudinal inserted or obstructed[16] artificial alv does induce hemolysis not as much by direct buffeting of the red cells as by the induction of cav tation [16] Experimental evidence supporting this iew comes from the studies of in itro mechanical fragility by Fok and Schubothe [13] who found that ed cells are not directly traumatized by rolling quartz beads but mainly by the induced turbulence

Further evidence for the influence of extreme intracardiac turbulence on red cells has come from ed cell survival tudies made by Brodeur and associates as ell as by ourselves,[16] on patients with different types of alvular heart disease. In our series compensated hemolysis was found in 17 of 35 patients, mainly in patients with aortic stenosis, but also in patients ith severe mitral stenosis nd even in 2 patients ith Grade IV aortic insufficiency I the case of valvular tenosis, the degree of transvalvular pressure gradient and the degree of calcification seem t be responsible for extreme intra cardiac turbulence, which results in cavitation and traumatic hemolysis of red cells. I the case of severe aortic insufficiency the studies of R binson clearly have demonstrated that, besides minor degree of turbulent blood flow the amount of regurgitant blood flow determines the frequency with which red cells are subjected to trauma. That the rate of hemolysis may bear relationship to the cardiac output has been pointed out by Sears and Crosby [17] A relationship between valvular heart disease and hemolysis is furthermore supported by the clinical observation by Dameshek and Roth of 63-year-old patient who most probably had mechanically in duced intravascular hemolysis due to calcified aortic and mitral stenosis and additional tricuspid stenosis.

Awareness of the entity of intra ascular hemolysis with schistocytosis after open-heart surgery is importa t and may even pro to be lifesaving, since, besides reducing the basal cardiac output, surgical correction of the defect is the only possible therapy if hemolysis is severe. Correction of other factors adding to nemia—infection and iron deficiency—will certainly be of benefit, but without reoperation, intravascular hemolysis will continue and may lead to irreversible renal damage. The best answer to this complication, certainly is prevention rather than correction.

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Book reviews

SURGICAL TREATMENT OF CONGENITAL HEART DISEASE. By Denton A. Cooley, M.D., and Grady L. Hallman, M.D., with Herbert R. Smith, M.A. Philadelphia, 1966, Lea & Febiger. 213 pages. Price $12.50.

This volume is intended by the authors to provide a description of the standard operative methods employed in their clinic in the treatment of congenital cardiac anomalies. Included in the text is a very short outline of the history, embryology, clinical, and cardiac catheterization findings, as well as a more detailed consideration of the techniques used in the repair of each lesion. A summary of the complications and results at one institution, the Texas Children's Hospital, is included at the end of each chapter. The text is clear and concise. The illustrations are adequate, and follow the text faithfully, although they are somewhat sketchy and the reader's imagination must fill in more of the detail than is ideal for this form of publication. The operative techniques described for most of the congenital anomalies are the ones in general use, and the bibliography should be useful in helping to fill in any voids in the text for those readers interested in greater detail.

Inclusion of a short paragraph devoted to the hemodynamic consequences of each of the various anatomic abnormalities would have been useful. In addition to each chapter and the absence of any consideration of the pathophysiology of congenital heart disease weakens the presentation to some extent. Over all, however, this book is a worthwhile addition to the surgical literature, and should serve as a helpful introduction to the subject for those physicians and surgeons unfamiliar with this area of surgery. For those more interested in the field, it is an interesting summary of current techniques and results in one large center.

RADIOLOGY IN WORLD WAR II. Edited by Arnold Lorentz Ahnfeldt, Colonel, MC, U.S.A., Kenneth D. A. Allen, Elizabeth M. McFetridge, and Mundell W. Stein, B.Sc., prepared and published under the direction of Lt. Gen. L. D. Heaton, Surgeon General, U. S. Army, Washington, D. C., 1966. 1087 pages. Price $8.25.

This is another good volume on the history of medicine in World War II. There is an excellent description of the equipment and radiologic personnel of the war. The text is supported by many good photographs, illustrations of lesions, a description of the case loads and the role of radiology in the induction station and in the field. The problems of training, transportation, role of consultants, and communication, as well as the clinical problems, are all well discussed. The reader is not only impressed with the excellent performance of the medical department of the U. S. Army during the most adverse conditions of a very mobile and world-wide war but by the excellent service rendered by the radiologists and their staffs under some of the most trying circumstances. The reviewer wonders about the reaction of the medical department to these problems and performances 100 years hence, during a future war. This is a good book and an important record of the history of United States medicine.

ADVANCES IN INTERNAL MEDICINE, Vol. XIII. Edited by William Dock, M.D., and I. Snapper, M.D., Chicago, Ill., 1967, Year Book Medical Publishers, Inc., 503 pages. Price $11.00.

The editors of this volume present advances in altitude and the pulmonary circulation, connective tissue polysaccharide metabolism and the pathogenesis of osteoarthritis, paired electric stimulation of the heart, observations on hepatic regeneration in man, comparison of indirect pressure measurements (Korotkoff) of arterial pressure with direct measurements, magnesium metabolism, urolithiasis, radioimmunoassay of polypeptide hormones, and current status and implications of serotonin in clinical medicine. These are important and interesting problems and the authors of the various sections are experts in their fields. As customary, the presentations are supported by good bibliographies. This volume is a very good one. It should interest not only internists but all physicians and students of medicine.

HEARTS—THEIR LONG FOLLOW-UP. By Paul Dudley White, M.D., and Helen Donovan. Philadelphia, 1967, W. B. Saunders Company. 357 pages. Price $12.00.

This book summarizes the follow-up of patients who were seen for many years by Dr. White. The types of diseases are quite variable. Many of the patients were children and young adults. This type of follow-up from Dr. White's private patient file is extremely important since it indicates the prognosis of cardiac disease still seen today. The book is divided into 20 chapters which group the patients with respect to the etiologic diagnosis as well as clinical states such as arrhythmias, congestive heart failure, and centenarians. Autopsy data are included in some of the case reports. This is an interesting book which reflects some of Dr. White's ideas on clinical cardiology as well as some of his experiences with his patients. The book also includes Dr. White's ideas on prognosis, the most difficult aspect of medicine.

AUSCULTATION OF THE HEART Ed. 2. By Abe Ravin, M D Chicago Ill., 1967 Year Book Medical Publishers, Inc., 262 pages. Price $8 00.

This small book is written in a style which is simple and clear and makes for easy relaxed reading. In general, complex areas and areas of controversy are avoided or are summarized succinctly. Basically this reviewer agrees with the factual information and interpretations as presented. A few subjects which could profit from clarification are late systolic clicks, late systolic murmurs, papillary muscle dysfunction, and papillary muscle rupture.

This book can certainly be recommended to all beginners in the study of cardiac auscultation. Most of the information presented, however should be well known to the experienced physician and cardiologist.

CLINICAL EXAMINATION OF THE JUGULAR VENOUS PULSE By Arnold L. Colman M D Springfield Ill. 1966, Charles C Thomas, Publisher 183 pages. Price $10 50.

There is increasing interest in the jugular venous pulse and this is good. With the introduction of the electrocardiograph and the passing of the Mackenzie polygraph the jugular pulse received very little interest until recently. This pulse reflects volume and pressure changes in the right side of the heart. Its characteristics are influenced by heart disease which modify hemodynamic phenomena. Doctor Colman describes the jugular venous pulse in various types of heart diseases. This pulse is particularly valuable in teaching and in understanding heart disease. Unfortunately when the physician needs assistance in diagnosis the jugular pulse offers little assistance. As is usual in such a presentation the classically characteristic pulses are shown. Such patients usually offer little difficulty in diagnosis anyway. Doctor Colman, as is true of others, says little about the cases that overlap with the normal or with patients with other diseases. Nevertheless, this is a good book in which the classical characteristics of the jugular pulses of various diseases of the heart are described. The illustrations are good, the bibliography is fairly complete, and the atlas of venous pulses tracings is a nice part of the book.

HEART DISEASE IN INFANCY AND CHILDHOOD John D Keith, M D Richard D Rowe, M.B., F.R.C.P and Peter Vlad, M D New York, and London, The Macmillan Co., 1239 pages. Price $35 00.

This is a very good textbook. As expected, it is concerned mainly with congenital defects of the heart and great vessels. Unfortunately acquired heart disease receives little attention. The chapter on heart disease in anemia is covered in three pages and cardiac disease due to malnutrition is essentially ignored. It is hoped that acquired heart disease will be discussed more fully in the next edition. When the entire world is considered, infections, anemia and malnutrition account for most of the heart disease in infants and children. This is certainly true in tropical countries. Nevertheless, the authors have produced an excellent book for pediatricians and all cardiologists. The chapters on examination of the heart and the congenital diseases are very good. This is a fine book which should be owned by all pediatricians and cardiologists and readily available to students. It is well organized in a textbook fashion clearly written, and nicely illustrated. A fairly complete bibliography is appended to each chapter.

CARDIOVASCULAR ROENTGENOLOGY A VALIDATED PROGRAM. By Charles M Nice M D Ph.D New York, 1967 Harper and Row Publishers, Hoeber Medical Division, 260 pages.

This is a good book for students and beginners in the field of cardiovascular diseases. Dr Nice has introduced a rather good approach to the interpretation of the roentgenograms of the heart and lungs not only diagnostically but physiologically and hemodynamically as well. The chest films reproduced are very good and the associated statements to be completed were well organized. By this approach, Doctor Nice forces his reader to think as he proceeds with the study of the illustrations. He presents the common congenital defects and acquired types of heart disease. This is a good book, although there are a few minor careless errors in the book such as the "invisible arrow in figure 36b on page 204 statement 472

CONGESTIVE HEART FAILURE. By Ralph M. Myerson M D and Bernard H Pastor M D St. Louis 19 The C. V. Mosby Company 174 pages. Price $12.85

Myerson and Pastor have described very briefly the clinical problems related to congestive heart failure They have avoided a detailed discussion of *the mechanism of congestive heart failure, for* they wrote their book for the clinician in practice. The chapter on the normal cardiovascular system is presented briefly (18 pages) but this chapter contains only a few ideas. The second chapter on the etiology and pathogenesis of congestive heart failure is quite incomplete (13 pages), but so is our knowledge whereas, the chapters on diagnosis and treatment are most extensive. This short book should interest clinicians.

DER SAUERSTOFFVERBRAUCH DES NORMO- UND HYPOTHERMEN HUNDEHERZEN VOR UND WAHREND VERSCHIEDENER FORMEN DES INDUZIERTEN HERZSTILLSTANDES. Oxygen consumption of the normo- and hypothermal canine heart before and during different types of induced cardiac arrest By Karl Bonhoeffer Basel and New York 1967 S Karger 73 pages.

This small book is actually a large experimental communication, perhaps too difficult to publish in the same detail in a periodical cardiological journal. It follows the typical presentation of an experimental paper Introduction (p. 1 2) Method

(p. 3-17) Results (p 18-47) Discussion (p 48-66) Summary (p 68-70) and References (p 71 73). The brief Introduction summarizes in tabular form the large discrepancies i the measurements (perhaps due t lack of standardization) of ml O consumption of 100 grams mammalian heart A method was developed for determination of the O consumption of the perfused canine heart i uits from coronary flow and A V differenc The tech w l error of measurement of O tension is so small (0 5 t 1 per cent) as t be lmost negligible The method made t possible t recognize steady stat of O consumption at y time during the experiment and t determine the O consumption t any temperat re The following conditions were estigated H pothermia cardiac arrest induced by increase of extracell lar potassium concentration ardiac rrest produced by de crease of the extracellula sodium and calcium conce tration ith nd ithout simultaneous administration of 3 per ent Novocain and cardiac arrest produced by addition of Novocain t the perfusion fluid ithout imultaneous de crease of the extrac llular potassium concentra tion Effect of m o rdial edema coronary resist nce and epinephrine were also investigated.

It is not possible t discuss in y detail the interesting results in the limited space of this review therefore few examples may suffice for illu tr tion As rule even t 5° C there is till lectrical activ t and only the pper limit of the myocardial O_2 consumption is determined by the temperature At 25° C it is about 2 milliliter per min t per 100 grams Increase of extracellular potassium concentration with cardiac rrest in reases the O_2 consumption nd the increase of metabolism by epinephrine is maintained The O_2 consumption in cardiac arrest produced by decrease of extracellular sodium concentration or Novocai administration is t 35° C 0 65 milli liter per minut per 100 grams ith Q increasing from Q_{35-25} = 1 55 t Q ... = 2 1 I this type of cardiac arrest the effect of epinephrine is abolished O_2 consumption depends lso on the dura tion of the perfusion hich declines so rapidly during the first 15 min tes that no steady state could be obtained The main over-all result of these series is the demonstration of the possibility of decreasing the O_2 consumption by combination of hypothermia ith one or the other type of cardiac arrest t a fairly ell reproducible minimum These data agree ith investigations of the naerobic metabolism and surv... al experiments.

A PSYCHOLOGICAL APPROACH TO HEART DISEASE. B Jacob Samuel Lhit, Ph D New York, 1967 Institut of Applied Psychology Inc., 128 pages. Price $3 95

This is short book concerned ith the influence of the mind and central nervous system on the hearts of patients ith heart disease as ell as their reactions to their disease nd problems of lif Doctor Lhit as prompted to write this book after mild heart ttack hich he developed in Hong Kong The author emphasizes the influence of emotional stress produced by life situations. The well-trained cardiologist and physician will find little of value or newness in this book. A large percentage of the references in the bibliography are from lay publications. This book will find its best use mong patients.

Books received

CARDIOVASCULAR RESEARCH January 1967 Edited by Joh Shillingford London 1967 British Medical Association Price $10 00

CLINICAL PHONOCARDIOGRAPHY By Deuchar Princeton N J 1965 D V Nostrand Co. Inc 144 pages Pric $3 75

DIABETES FOR DIABETICS By George F Schmitt. Miami 1965 Diabetes Press of America, Inc 237 pages. Price $5 95

DIAGNOSTIC PRATIQUE DES CARDIOPATHIES CONGÉNITALES Ed 2 By Jean Bret Paris 1962 L'Expansion Scientifique Française, 181 pages.

ESSENTIALS OF PAED ATR C CARDIOLOGY By A. W Venables. Springfield Ill 1964 Charles C Thomas 164 pages Price $6 75

THE ELECTROCARDIOGRAPHIC EXERCISE TEST Burbank, Calif M D Electronics.

ELECTROPHYSIOLOGY OF THE HEART Edited by B Taccardi and G Marchetti. I ternational Symposium held t the I t tuto di Cardiologia Sperimentale Dei Servizi Scientific Simes, Milan, Italy New York, 1965 Pergamon Press, The Macmillan Co 344 pages Price $15 00.

ENGINEERING IN THE PRACTICE OF MEDICINE. By Bernard L. Segal and David G Kilpatrick P.E. Baltimore, 1967 The Williams & Wilkins Co., 482 pages Price $20.00

LE JOURNAL DE MÉDECINE DU MAROC (REVISTA MEDICA DE MARRUECOS), Tome II N 9 Edited by M Benmani. Casablanca Redaction et Administration Nov 1966

NORMALER UND HOHER BLUTDRUCK UND KARDIOVASKULARE MORTALIT T BEI VERSCHIEDENEN VOLKERN By Robert Stigler Darmstadt 1964 Dr Dietrich Steinkopff Verlag, 294 pages.

PRINCIPLES OF CHEST ROENTGENOLOGY—A Programmed Text. By Benjami Felson, Aaron S. Weinstein nd Harold B Spitz. Philadelphia, 1965 W B Saunders Company 221 pages. Price $6.00

PROCEEDINGS OF THE THIRD INTERNATIONAL CONFERENCE ON HYPERBARIC MEDICI E—Publication No. 1404 Washington, D C., N tional Academy of Sciences, 1966 pages. Price $15.00.

AUSKULTATION DES HERZENS UND IHRE HAMODYNAMISCHEN GRUNDLAGEN By Hans Blomer München, 1967 Urba and Schwarzenberg 318 pages.

Cardiologia—Vol 29 Supplementum II 1966, Symposium on Propanolol (Inderal), the First Adrenergic Beta Receptor Blocking Agent in Practice. Chairman R. Hegglin and J. L. Rivier Basel, 1966 S. Karger 89 pages.

Collana di Monografie Cardiologiche, No 18, La Gravidanza nelle Cardiopatie Chirurgiche. By A. Actis Dato G B Panero, and R. Gentilli Milano, 1966 Recordati-Industria Chimica Farmaceutica, 119 pages.

Clinical Phonocardiography and External Pulse Recording. By Morton E. Tavel. Chicago. 1967 Year Book Medical Publishers 230 pages Price $10.00.

The Human Heart—The Layman guide t heart disease. By Brendan Phibbs Lane Craddock, George Griffith, Robert T P trick, nd Colin H M W lker St. Louis, 1967 The C. V Mosby Company 253 pages. Price $4 95

Neuzeitgebiete der Elektrokardiologie. By Ernst Schubert. Jena, 1966, Gusta Fischer Verlag 275 pages.

Announcement

JANE NUGENT COCHEMS COMPETITION. The University of Colorado School of Medicine announces the Sixth Annual Cochems Competition, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper in the field of "Thrombophlebitis and Basic Vascular Problems." Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease, particularly those associated with thrombosis, but not necessarily restricted to it.

The competition is open to all persons holding the doctoral degree and entries must be received in triplicate, including all charts, illustrations, and photographs, on or before *November 15, 1967*. For income tax reasons eligibility is limited to those physicians who are subject to U. S. income tax regulations.

The Colorado National Bank of Denver, Trustees under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges appointed by the Dean are Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine in St. Louis, and Dr. Michael F. De Bakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine. Decisions of the judges are final, and they may elect at their discretion not to award the prize.

Papers submitted in the competition may not be published until after the winner has been announced early in 1968. At that time the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that sponsors and judges of the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation "Awarded the Jane Nugent Cochems Prize."

No entry blank or application form is required. There are no restrictive rules regarding length or format of the manuscript, joint authorship, or inclusion of such materials as pictures, charts, figures, etc. It is not required that the paper include results of original experimental work, nor that it be based on personal clinical experience. All manuscripts must be typed with double spacing and each copy together with accompanying illustrations, etc., must be submitted in a folder or cover. On request, the original copy of the manuscript will be returned if accompanied by a stamped, addressed envelope. Papers will be judged on originality, content, clarity, and critical value.

Inquiries regarding the competition and all manuscripts should be submitted to Dr. John J. Conger, Vice President for Medical Affairs and Dean, School of Medicine, University of Colorado Medical Center, 4200 E. Ninth Ave., Denver, Colo. 80220.

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Editorial

The use and abuse of cerebral angiography in the diagnosis of strokes

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Cerebrovascular disease is nowadays one of the major causes of death in the community; in addition it is responsible for a great deal of morbidity. Furthermore, death and disablement from cerebrovascular disease are not confined to patients in the eighth and ninth decades; increasing numbers of patients are afflicted from the fifth decade onward.

In the face of this toll, it is not surprising that energetic attempts are being made to combat the disease in a variety of ways but especially by anticipating the development of a completed stroke and endeavoring to prevent its occurrence. In order to do this, lesions of the arteries must be discovered before infarction has occurred, and this can be done only by visualizing the arteries by means of angiography. There has been, and still is, a considerable reluctance to use angiography in the diagnosis of degenerative cerebrovascular disease for fear of precipitating the very lesion one is trying to prevent. But increasing experience has shown that in competent hands and properly selected cases, the value of angiography far outweighs the hazard.

Failure of the blood supply to the brain may arise from a variety of causes not limited to the cerebral vessels. Factors in the heart and in the blood may play their part in producing cerebral ischemia. These causes cover so wide a field that some demarcation of the subject must be imposed. It is not, however, logical to limit the field to the cerebral vessels within the skull. The frequency with which cerebrovascular symptoms are associated with stenosis of the carotid and vertebral arteries emphasizes the impossibility of considering the cerebral vessels independently of their major arteries of supply. Nowadays, therefore, it is customary to consider the cerebral vascular tree from the aortic arch onward. Stenosis of any of the three branches of the aortic arch, by acting as a site for the formation of emboli or by interfering with blood flow, can have the same effect as a stenosis at a more distal site.

This conclusion influences decisions about the angiographic investigation of degenerative cerebrovascular disease. Angiography of part of the periphery of the cerebrovascular tree cannot be satisfactory. If no abnormality is found, the possibility of a more proximal lesion cannot be excluded.

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if a lesion is found it cannot be ascertained whether it is acting alone or in combination with other lesions to produce the clinical situation. Therefore the investigation of degenerative cerebrovascular disease must begin at the aortic arch and proceed peripherally in the light of what may be found. It is in implementation of this conclusion that four vessel angiography usually performed via a catheter sited in the aortic arch and elsewhere in the vascular tree has been developed.

The application of this principle is by no means simple. Whereas it is possible with the use of automatic cassette changers carrying large films to obtain serial roentgenograms of the arterial tree from the aortic arch to the brain this method does not permit each part of the tree to be seen in the best projection. Moreover because of the large amount of contrast medium required for each injection this limitation cannot be overcome by multiple injections in different positions. Certain priorities have to be determined for each patient and this can be done only by close collaboration between the physician and the radiologist.

For transient ischemic attacks which are not obviously due to a nonarterial cause or completed strokes which are likely due to infarction the first step should be to assess the state of the extracranial arteries. These are the vessels from which emboli may have arisen these are the sites at which constrictions may have reduced cerebral blood flow and these are the vessels within reach of the vascular surgeon.

Visualization of these vessels is best achieved by intra arterial catheterization. A catheter may be introduced by a variety of routes (brachial axillary subclavian or femoral) but among these the axillary artery (especially the right[5]) and the femoral artery seem to be the most advantageous. Introduction of the catheter via the right axillary artery permits good visualization of the right side of the vascular tree and in two thirds of the cases of the left side as well. Moreover adequate films of the right side of the intracerebral circulation alone can be obtained by positioning the catheter in the innominate artery.

Study of the left side of the extracranial arterial tree in those cases not visualized during catheterization of the right axillary artery is best achieved by the femoral route. This permits selective catherization of either the left carotid or subclavian arteries. Femoral catheterization in an appreciable proportion of patients with advanced atherosclerosis is difficult because the tortuosity of the iliac arteries prevents the introduction of the catheter into the aorta.[6] Nevertheless, when the clinical story or the presence of a bruit indicates that the patient has a stenosis of the left internal carotid artery at its origin the method of first choice may be catheterization via the femoral artery. If on the other hand after catheterization of the right axillary artery the bifurcation of the left common carotid artery is brought under suspicion but is inadequately seen direct needle puncture of that carotid artery may be undertaken. Each patient must be considered individually the likely sites of lesions must be determined and then the extent and route of the investigation specifically planned.

Arterial catheterization is not without hazard. The most common complication is thrombosis following damage to the vessel through which the catheter is introduced although in competent hands the risk is small. An extensive survey showed a mortality rate of 0.06 per cent and an incidence of serious complications of 0.7 per cent in 11,402 procedures.[7] These figures are acceptable in view of the serious nature of the condition under investigation. Direct needle puncture of an artery is also hazardous occlusion of the artery is the most common complication. This may be due to thrombus formation at the site of the needle puncture (sometimes with subsequent embolization) or from elevation of an atheromatous plaque by the needle in rare instances or after subintimal dissection of the arterial wall.[8] Moreover direct puncture of an artery has the limitation that only a single artery is visualized. Multiple punctures are required to secure complete visualization of the extracranial vascular tree and even then its more proximal segments are not included. The surgeon operating upon a carotid stenosis needs to know about the

state of the contralateral carotid artery and preferably that of the vertebral arteries as well. Catheterization of the aortic arch supplemented when necessary by direct puncture of a single artery about which there may be specific question is the best line of approach. When the clinical situation indicates that detailed study of the intracranial vessels is the pre-eminent requirement, direct puncture of a single artery is preferable.

The effort to prevent strokes has increasingly focussed attention upon the hemodynamic aspects of the cerebral circulation and upon alterations in cerebral blood flow which may arise in a variety of situations. Compression or kinking of arteries may arise during movement of the neck, especially in patients with cervical spondylosis. The subclavian steal syndrome has been increasingly recognized as a cause of intermittent vertebrobasilar ischemia.[1] These situations can be diagnosed only by angiography and preferably by techniques which permit the contrast medium to be observed throughout its passage through the vascular tree. Thus rapid serial angiography, cinefluoroscopy, and video tape are increasingly employed in the diagnosis and study of cerebrovascular disease.

The multiplicity of techniques now available for the angiographic investigation of degenerative cerebrovascular disease greatly increases diagnostic achievement and in turn therapeutic potential. It could, however, readily lead to abuse. Not every patient with degenerative cerebrovascular disease should be subjected to angiography.

For many patients the stroke has replaced pneumonia as the "old man's friend" by terminating a life which had already become a burden. The enthusiastic investigation of such patients is misplaced; their lives should be allowed to move to a peaceful and dignified close. But strokes increasingly afflict younger patients (and in this respect it should be remembered that biological and chronological age are not always the same) and the possibility that something may be done to minimize the damage already done or to prevent further damage, justifies investigation. The occurrence of a transient ischemic attack in both older and younger patients is again a strong indication for investigation, for this type of incident is often a forewarning of a more serious stroke which may be prevented by timely intervention. The presence of extracranial arterial bruits is a further indication for investigation, as this sign increases the probability of finding a lesion amenable to surgery. Finally, it should not be forgotten that in any series of patients presenting with a stroke or even with transient ischemic attacks, a small percentage will have a cerebral neoplasm.[11] Cerebral angiography is often, though not always, helpful in detecting these cases.

Wisely and skillfully used, cerebral angiography can supply information essential to the proper management of degenerative cerebrovascular disease without undue risk. This use demands, first, careful clinical assessment of the patient both as to the probable site of his lesion or lesions and his general cerebrovascular and cardiovascular status. Second, it requires close collaboration between the physician and the radiologist in planning the extent and the route of angiography in order to obtain the maximum relevant information with the minimum of hazard. Used in this manner, angiography undoubtedly makes a major contribution to the management of cerebrovascular disease.

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Clinical communications

Atrial function after cardioversion

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The success of transient D.C. depolarization in restoring sinus rhythm in patients with atrial fibrillation is now well established. Electrocardiographic evidence of restoration of normal sinus rhythm is often assumed to be accompanied by the return of atrial contraction, but it has previously been shown that this is not necessarily true. The correlation, or lack of it, between the return of normal atrial excitation and effective atrial systole is clearly of importance. This paper records observations on the acute hemodynamic changes after cardioversion with particular reference to atrial activity.

Subjects and methods

Eighteen patients with atrial fibrillation or atrial flutter were studied (Table I). Thirteen had chronic rheumatic valve disease; the mitral valve was predominantly affected in 12 patients, and the aortic valve in 1. Three patients had ischemic heart disease. One patient had mitral incompetence due to rupture (presumably ischemic) of the chordae tendineae and 1 had been treated for thyrotoxicosis. Left heart catheterization was a necessary investigation in 14 patients, and in these cases cardioversion was attempted during the investigation. In 11 patients left atrial pressure tracings were obtained before and after cardioversion. In 8 of these patients, left ventricular pressures, and in 10 right atrial pressures, were obtained before and after cardioversion. In 6 other patients, right atrial pressure tracings were obtained by means of fine polythene tubing inserted percutaneously from a cubital fossa vein. In one of these patients a satisfactory wedge tracing of the pulmonary capillary venous pressure was obtained.

When all catheterization procedures were complete the patient was left undisturbed for 15 minutes before measurements of basal pressure were taken. Between two and five determinations of basal cardiac output were then made. The electrocardiogram was monitored and recorded throughout the procedure.

The patients were lightly anesthetized with intravenous methohexitone (Brietal) given over 20 seconds in a dose of 1.2 mg

Funds for the purchase of the Lown Cardioverter used in this study were made available by the British Heart Foundation.
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Table I. Clinical features and details of cardioversion

Case number	Diagnosis	Rhythm	Duration of arrhythmia	Shocks given (joules)	Success (S) or failure (F)	Period before reversion to arrhythmia
1.	Ischemic heart disease (myocardial infarct 3/12 ago)	Atrial flutter	3 mo.	50 100 200 300	S	No follow-up
2.	Mitral valve disease with dominant stenosis	Atrial fibrillation	4 wk.	50 100 200 300	F	—
3.	Ischemic heart disease: Hypertension	Atrial fibrillation	4 mo.	50 100 200 300	F	—
4.	Mitral stenosis	Atrial fibrillation	10 wk.	50 100 200 300	F	—
5.	Mitral valve disease with dominant incompetence	Atrial fibrillation	1 yr	50 100 200 300 400	F	—
6.	Ischemic heart disease	Atrial flutter	12 days	50 100 200	S	No follow-up
7	Mitral incompetence	Atrial fibrillation	10 days	50 100	S	4 wk.
8.	Nonrheumatic mitral incompetence (ruptured chordae)	Atrial fibrillation	4 mo.	50 100 200 300	S	8 days
9.	Mitral stenosis	Atrial fibrillation	4 mo.	50 100 200 300	S	3 wk.
10.	Aortic stenosis. Mitral stenosis	Atrial fibrillation	3 yr	50 100 200	S	4 mo.
11.	Mitral valve disease with dominant stenosis	Atrial fibrillation	4 mo.	50 100 200	S	4 wk.
12.	Mitral valve disease with dominant stenosis	Atrial fibrillation	10 days	50 100 200	S	Sinus rhythm at 2 mo.
13.	Mitral incompetence	Atrial fibrillation	3 wk.	50 100	S	—
14.	Mitral stenosis	Atrial fibrillation	3 yr	50 100 200	S	No follow-up
15.	Mitral valve disease with dominant stenosis	Atrial fibrillation	2 yr	50	F*	—
16.	Thyrotoxicosis (treated)	Atrial fibrillation	4 yr	50 100 200	S	10 wk.
17	Mitral incompetence. Tricuspid stenosis	Atrial fibrillation	2 yr	50 100 200 300	S	Sinus rhythm at 7 wk.
18.	Mitral stenosis†	Atrial fibrillation	4 mo.	50 100 200	S	1 wk.

*Bradycardia and S-T segment elevation developed and procedure was abandoned.
†Mitral valvotomy 1 week previously.

per kilogram of body weight. Amnesia was maintained through the use of 20 per cent oxygen and 80 per cent nitrous oxide. In 8 patients determinations of cardiac output were repeated at between 30 and 60 seconds and again between 3 and 4 minutes after the end of the injection of methohexitone. Brachial arterial pressure tracings were recorded continuously for 2 minutes before and during and for 5 minutes after the end of the injection of methohexitone.

Cardioversion was then attempted using an anteroposterior D.C. countershock delivered from a Lown Cardioverter. The number and strength of shocks given were recorded (Table I). A single shock of each of the following strengths was given until cardioversion was successful or the strongest shock had been given: 50, 100, 200, 300, 400 joules. After the attempted cardioversion determinations of cardiac output and measurements of pressure were repeated approximately every 5 minutes, observation being continued for periods varying from 30 to 60 minutes after the end of the cardioversion procedure. The administration of nitrous oxide and oxygen was stopped immediately after the last shock had been delivered and the patients were allowed to recover from anesthesia spontaneously. In all cases, consciousness returned within 3 minutes after the oxygen and nitrous oxide had been stopped.

Digitalis was withdrawn 48 hours before the procedure. No quinidine was given. Premedication in all cases consisted of

Table II Hemodynamic effects of anesthesia (mean values for the group)

	Basal	½-1 Minute after induction of anesthesia	3-4 Minutes after induction of anesthesia
Mean heart rate (per min.)	96	113	120
Mean cardiac index (L./min./M²)	2 4	2 1	2 0
Mean stroke index (ml./M²)	25	19	17

20 mg of papaveretum and 25 mg of promethazine.

The pressure tracings were obtained by means of Statham P23Gb strain-gauge transducers with New Electronics Products amplifiers and photographic recorder Cardiac outputs were determined by the dye-dilution technique using indocyanine green and the Waters X 301 densitometer and earpiece The dye curves were recorded on the Mingograf 81 recorder (Elema Schonander) Injections of precisely known amounts of dye were made from a finely graduated syringe using approximately 2 ml. of dye solution with a concentration of 5 0 mg per milliliter The injection was given by hand and each injection was completed within 1 second The catheter tubing was kept filled with dye between injections. The dye was injected into the left atrium when studies on the left side were performed and into the right atrium in the other cases. Calibration of the earpiece against brachial arterial samples was performed using at least four points scattered throughout the whole range of the recorder deflection by a method described elsewhere.[8]

Results

Effects of anesthesia Since all patients were anesthetized and the studies were completed within 1 hour of cardioversion any hemodynamic changes occurring as a consequence of anesthesia are obviously relevant. The changes are described in detail elsewhere. The mean values for heart rate (HR) cardiac index (CI) and stroke index (SI) in Cases 1 5 and 12 are given in Table II Between 30 seconds and 1 minute after the end of the injection of methohexitone there was an increase in the mean HR from 96 to 113 per minute. At the same time the mean CI fell from 2.4 to 2 1 L./min /M² and the SI fell from 25 to 19 mL/M Between 3 and 4 minutes after the end of the injection of methohexitone the mean HR had risen to 120 per minute the mean CI had fallen to 2.0 L./min /M and the mean SI had fallen to 17 ml./M

Effects of D C countershock All measurements recorded as "before cardioversion (Table III) were taken before anesthesia. All measurements recorded as after cardioversion (Table III) are the means of values taken between 10 minutes and 1 hour after the end of the procedure. Thus all post-cardioversion values are compared with pre-cardioversion pre anesthetic values.

SUCCESS RATE (Table I) Among the 18 patients 13 were successfully restored to sinus rhythm 4 failed to be converted after receiving four or five shocks, and in one (Case 15 Tables I and III) the procedure was abandoned after the first 50-joule shock when he developed bradycardia and S-T segment elevation. Excluding this patient, the success rate of the procedure was 76 per cent. At the most recent assessment only 2 patients were still in sinus rhythm at periods of 7 weeks and 2 months after cardioversion.

PRESSURE TRACINGS (Table III)

Right Atrium Mean right atrial pressures were slightly increased after successful cardioversion in 3 patients, were unchanged in 3 and were reduced in 7 Of 3 instances in which cardioversion failed mean right atrial pressures were unchanged in 2 and increased in 1

Of 13 patients in whom cardioversion was successful 12 developed an "a wave in the right atrium An example is shown in Fig 1 Of 10 patients in whom cardio-

Table III Hemodynamic effects of cardioversion

Case n mber	Degree of left atrial enlargement radiologically	Success (S) or fail re (F) of cardioversion	Before (B) and after (A) cardioversion	Heart rate (beats/m)	Cardiac index (L./min./M)	Stroke ndex (ml./M)
1	Nil	S	B	112	2 8	25
			A	83	2 45	30
2	Moderate	F	B	94	2 5	27
			A	96	2 6	27
3	Nil	F	B	94	2 5	27
			A	90	2 1	23
4	Moderate	F	B	89	1 5	17
			A	81	1 5	19
5.	Gross	F	B	83	2 05	25
			A	96	1 8	19
6.	Nil	S	B	142	2 1	15
			A	82	1 95	24
7	Gross	S	B	102	3 6	35
			A	86	4 0	47
8.	Moderate	S	B	78	1 35	17
			A	84	2 1	23
9	Gross	S	B	68	2 3	34
			A	72	2 3	32
10.	Gross	S	B	74	3 5	47
			A	71	3 6	51
11	Slight	S	B	138	2 45	18
			A	100	2 85	29
12	Moderate	S	B	115	2 75	24
			A	86	2 6	30
13	Moderat	S	B	98	3 8	39
			A	86	3 7	45
14	Moderate	S	B	81	3 0	37
			A	85	4 2	49
15.	Slight	F†	B	70		
			A	58		
16.	Nil	S	B	72	2 4	33
			A	54	3 1	57
17	Slight	S	B	87	2 6‡	30
			A	78	2 8	36
18.	Moderate	S	B	108		
			A	97		

*In this column, where two figures are given, the first one indicates pressure 10 minutes after cardioversion, and the second indicates
†Procedure bandoned after first shock hen brady cardia and S-T segment elevation developed.
‡Absence of lef atrial contraction subsequently confirmed at operation.
§Pulmonary capillary venous (wedge) tracing.
¶Fick outputs.
Note: Cardiac index before cardioversion is the mean of readings taken before anesthesia. Cardiac index after cardioversion is the mean

version was successful 2 showed increased and 2 showed decreased right atrial v" waves after cardioversion In the other 6 patients there was no change in the v wave In 3 instances in which cardioversion failed the v wave was unchanged

Left Atrium Of 8 patients in whom cardioversion was successful mean left atrial pressures were increased in ? un changed in 1 and reduced in 5

Of 4 patients in whom cardioversion failed mean left atrial pressures (MLAP) were increased in 3 and reduced in 1 In all 3 patients in whom the mean left atrial pressure rose there was a fall toward the basal level within 30 minutes.

Height of wave above nadir of y descent (mm Hg)		*Mean pressures (mm Hg)*		*Left ventricular end-diastolic pressure* (mm. Hg)*	*Alterations in size of atrial "v" waves after cardioversion*	
Right atrium	*Left atrium*	*Right atrium*	*Left atrium*		*Right atrium*	*Left atrium*
—	—	9	—	—	Nil	—
1 0	—	6	—	—		
—	—	5	12	8	Nil	Nil
—	—	8	23→17*	19→12*		
—	—	—	—	—	—	—
—	—	—	—	—		
—	—	9	40	7	Nil	Nil
—	—	9	30	—		
—	—	10	15	—	Nil	Nil
—	—	10	29→17*	—		
—	—	5	—	—	Nil	—
3 5	—	6	—	—		
—	—	9	17	10	Nil	Nil
3 0	2 0	8	20	20→13		
—	—	10	21	15	Increased	Increased
3 0	4 0	7	30	17		
—	—	12	24	10	Decreased	Decreased
1 5	0‡	9	19	12		
—	—	18	27	18	Increased	Decreased
0	0	18	25	14→22		
—	—	15	28	6	Nil	Decreased
1 5	1 5	6	22	8		
—	—	10	—	—	Nil	—
1 0	—	12	—	—		
	—	13	24	14	—	Decreased
2 0	0	11	19	20→16		
—	—	4	13	14	Nil	Nil
1 7	2 0	3	11	8		
—	—	—	15	—	—	Nil
—	—	—	18→16	—		
—	—‡	6	9‡	—	Nil	Nil‡
1 3	1 0	6	9‡	—		
—	—	4	—	—	Nil	—
3 0	—	7	—	—		
—	—	8	—	—	Decreased	—
1 0	—	8	—	—		

pressures between 20 and 30 minutes after cardioversion

of readings taken after cardioversion, at least 10 minutes after the procedure. All patients were conscious after 5 minutes.

Of 8 cases of successful cardioversion, left atrial "a" waves (Fig 2) developed in 5 and did not develop in 3 (Fig 3) Thus there were patients (Cases 9 and 13 Table III) who developed right atrial "a" waves but did not develop left atrial "a" waves

Of 8 cases of successful cardioversion, the size of the left atrial "v" wave was decreased in 4 increased in 1 and unchanged in 3 In none of 4 cases in which cardioversion failed was there any change in the left atrial "v" wave

Left Ventricle Changes in left ventricular end-diastolic pressure in relation to cardioversion were measured in a total of

8 patients. Of 7 patients in whom cardioversion was successful 5 had increased end-diastolic pressures after the procedure 1 had an appreciable fall and 1 showed a fall initially followed by an increase after approximately 20 minutes. In 1 case in which cardioversion failed there was a substantial increase in left ventricular end-diastolic pressure initially with a return toward the basal value after 20 minutes (Case 7 Table III)

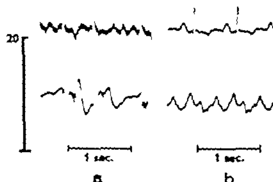


Fig 1 Case No. 7 Right atrial pressure tracings before ( ) and after (b) successful cardioversion The pressure scale is millimeters of mercury

HEART RATE (HR) The heart rates given in Table III were measured simultaneously with the determinations of cardiac output. Ten of 13 patients in whom cardioversion was successful showed a reduction in ventricular rate after the procedure (Fig 4,b) The other 3 patients showed minor increases In these successful cases the HR per minute before cardioversion ranged from 68 to 142 (mean 98) The values after cardioversion ranged from 54 to 100 The over all mean change in HR in these cases was −16 per cent.

Of 5 patients in whom cardioversion failed 3 had reduced ventricular rates and 2 had increased ventricular rates after the shock. In most cases the changes were slight (Fig 4,c) The resting HR per minute before cardioversion ranged from 70 to 94 (mean 86) and after attempted cardioversion it ranged from 58 to 96 (mean 84) The mean change was −2 per cent.

CARDIAC INDEX (CI) Seven out of 12 successfully cardioverted patients had increased cardiac indices after cardioversion (Fig 5) Four patients had slight reductions in CI and in 1 there was no change In these 12 patients the resting CI before

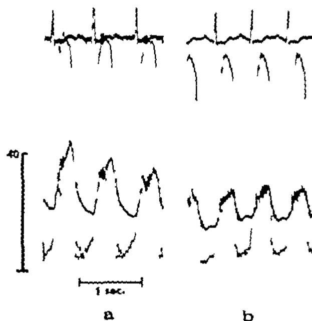


Fig 2 Case No. 11 Left atrial and left ventricular pressure tracings before ( ) and after (b) successful cardioversion. The pressure scale is in millimeters of mercury

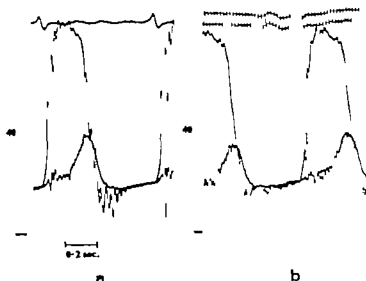


Fig 3 Case No. 13. Left trial and left ventricular pressure tracings before ( ) nd after (b) successful cardioversion. The pressure scale is millimeters of mercury

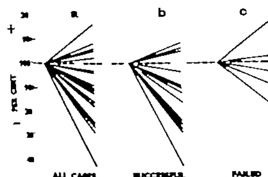


Fig 4 Change in heart rate after cardioversion.

cardioversion ranged from 1 35 to 3 8 (mean 2.7) L./min./M and after restoration of sinus rhythm it ranged from 1 95 to 4.2 (mean 3 0) L./min. M The over all change in these 12 cases was +9 per cent.

Of 4 cases in which cardioversion failed 1 showed no change in CI 1 showed a slight rise and 2 showed moderate falls. The values before cardioversion ranged from 1.5 to 2.5 (mean 2 1) L./min./M and after cardioversion they ranged from 1.5 to 2.6 (mean 2.0) L./m n./M[2] The over all change in these 4 patients was −5 per cent.

STROKE INDEX (SI) Eleven out of 12 successfully cardioverted patients had increased stroke indices after the procedure. In the 1 other case there was a small fall (Fig 6) The values before cardioversion ranged from 15 to 47 (mean 30) ml /M[2] After cardioversion the values ranged from 24 to 57 (mean 38) ml / M The change in the mean value was +27 per cent

Of 4 cases in which cardioversion failed 2 showed a reduction in SI 1 showed a slight rise and the fourth case showed no change (Fig 6) The values before attempted cardioversion ranged from 17 to 27 (mean 24) ml / M After attempted cardioversion the values ranged from 19 to 27 (mean 22) mL/M The percentage change of the mean was −8.

Discussion

The results described apply only to the early hemodynamic changes at rest after D C countershock all observations were made within 1 hour of the final shock.

In assessing the value of normal atrial activity several previous studies have compared hemodynam c measurements before and after quinidine con ersion. In such studies t is difficult to separate the effects of change in rhythm from the possible effects of qu nidine on the heart. In the present study the use of quinidine was avoided and digitalis was withheld for the 48 hours before the procedure.

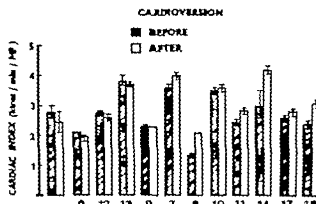


Fig 5 Mean cardiac index befor nd after cardioversion. The lines at the tops of the columns indicate the total scatter of the readings obtained Where no line is present single reading was obtained. The numbers at the bottoms of the columns are case numbers.

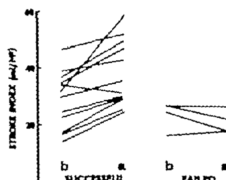


Fig 6 Stroke index before (b) nd after ( ) cardioversion

Effects of anesthesia The effects of anesthesia in our series are described in detail elsewhere The mean values give a clear picture of the general trend of the changes. Within 1 minute of completion of the injection of methohexitone there was an increase in heart rate accompanied by a fall in cardiac index and stroke index. By 3 to 4 minutes after the end of the injection there was a small additional increase in HR and small additional falls in CI and SI and when the arterial blood pressure was recorded this also fell The initial effects of anesthesia are important from two points of view First any increase in cardiac output occurring as a consequence of the restoration of sinus rhythm is likely to be underestimated in our early post-cardioversion measurements. Second ly it is possible that the tachycardia di minished cardiac output and reduced arterial pressure after anesthesia may render successful cardioversion less likely or may predispose to post-cardioversion arrhythmias.

Changes in right atrial p essure Of 13 successfully cardioverted patients in whom right atrial pressure tracings were recorded both before and after cardioversion 12 developed clearly indentifiable a waves indicating the return of effective right atrial contraction One patient (Case 10 Table III) had no discernible right atrial systolic wave despite the electrocardiographic evidence of the return of normal atrial contraction When no atrial a wave develops there is no atrial augmentation of right ventricular filling There is evidence [12,13] that the right atrial "a wave plays a part in tricuspid valve closure and that incompetence of the tricuspid valve may result from the absence of the a wave in atrial fibrillation. [13] In the present study cardioversion did not lead to significant changes in either right atrial v waves or mean right atrial pressures, such as might have occurred if pre-existing tricuspid incompetence had diminished on the restoration of sinus rhythm Thus there was no hemodynamically significant tricuspid incompetence as a result of atrial fibrillation in our series and this agrees with recent work. [6]

Changes in left atrial pressu e Five out

of 8 of our patients developed left atrial "a" waves after cardioversion but in 3 (Cases 9, 10, 13, Table III) normal electrical excitation of the atria was restored without evidence of the return of effective atrial systole. In one of these patients (Case 9, Table III) the absence of left atrial contraction was confirmed subsequently during mitral valvotomy. It is of interest that in 2 patients (Cases 9 and 13, Table III) right atrial "a" waves returned on the restoration of normal sinus rhythm despite the absence of left atrial "a" waves. This may be related to the predominantly left-sided disease in these patients as discussed elsewhere. Other authors[17] have noted that the atrial "a" waves may be poorly developed after the restoration of normal sinus rhythm in a case of long-standing atrial fibrillation. There is no proof that atrial myocardial shortening does not return in these patients but any shortening which does develop is insufficient to produce a detectable atrial systolic pressure wave. The size of the "a" wave will depend on left atrial size and myocardial compliance, as well as on the strength of left atrial contraction. Of the 3 patients who failed to develop left atrial "a" waves, 2 had gross, and 1 had moderate, left atrial enlargement radiologically. However, 2 patients with moderate (Cases 8 and 14, Table III) and 1 patient with gross (Case 7, Table III) left atrial enlargement did develop left atrial "a" waves.

Where no left atrial "a" wave develops there can be no atrial augmentation of ventricular filling or of mitral valve closure. Several authors have reported the development of mitral incompetence with the onset of atrial fibrillation.[6-20] Other workers have been unable to reproduce these findings,[21] and recently Braunwald and associates[22] have shown that a properly timed atrial contraction is not always essential for effective closure of the mitral valve in man. In our series, the left atrial "v" wave was decreased in 4, increased in 1, and unchanged in 3 cases. Even if this tendency toward a reduction in the height of the left atrial "v" wave is the result of more effective mitral valve closure in the presence of atrial contraction,[22] this could not have occurred in the 3 patients in whom no left atrial "a" wave developed.

Changes in left ventricular pressure. Five out of 7 patients had increased left ventricular end-diastolic (LVED) pressures 10 minutes after successful cardioversion. This could not be attributed to the return of left atrial contraction in all cases, for in 2 of the patients (Cases 9 and 13, Table III) no left atrial "a" wave developed. Furthermore, in a single case of failure of cardioversion, an appreciable increase in LVED pressure occurred. In only 1 instance was the increase in LVED pressure accompanied by more than a slight change in heart rate, and the increases in pressure could not therefore be explained on the grounds of greater diastolic filling times. It seems to be likely that the cardioversion shock, whether it is or is not successful, may alter the LVED pressure by affecting left ventricular function or distensibility. Reale[11] found a reduction in LVED pressure in most of his 12 cases after cardioversion. However, his pressure measurements were taken 30 minutes after cardioversion, and 3 of our patients who had raised LVED pressures 10 minutse after the D.C. shocks had more basal LVED pressures 10 to 20 minutes later.

Changes in cardiac output. In this study determinations of resting cardiac output were made before and after successful cardioversion in 12 patients and before and after failure of cardioversion in 4 patients. In 7 of the successful cases the cardiac indices were increased (ranging from 3 to 55 per cent) after cardioversion as compared with pre-cardioversion pre-anesthetic values (Fig. 5). In all but 1 of these cases there was an increase in stroke volume (Fig. 6). The greatest reduction in cardiac index recorded among the successful cases was 0.35 L./min./M.² The over-all mean change in cardiac index in our 12 cases was +9 per cent. Since we have shown that the cardiac index 3 to 4 minutes after anesthesia was less than that before anesthesia in 6 out of 7 cases, any residual hemodynamic effects of anesthesia which may have been present at the time of our post-cardioversion studies will result in an underestimation of the increase in cardiac output occurring after cardioversion.

It seems to be generally agreed[23] that

a significant number of patients have an increase in cardiac output after the conversion of atrial fibrillation to sinus rhythm. Some workers have recorded appreciable increases in cardiac output several days after cardioversion when no increases had been demonstrable immediately after the restoration of sinus rhythm.[14] This discrepancy has been attributed to the persistence of hemodynamic effects of anesthesia in the immediate post-cardioversion studies. However, Benchimol and associates[17] found no difference between outputs determined at ½ hour and those at 18-32 days after cardioversion in 3 patients. Graettinger,[18] studying 16 patients before and 1 hour after cardioversion, found a significant increase in cardiac output only in those patients in whom an appreciable reduction in ventricular rate occurred. There was no over-all correlation in our results between change in cardiac output and change in heart rate (Fig. 7).

Relationship of change in cardiac output to change in atrial activity. There were 8 patients (Cases 7, 11, 13, 14, 16, Table III) in our series in whom both determinations of cardiac output and left atrial pressure tracings were obtained. In 3 of these 8 patients no recognizable left atrial systolic wave developed, and the changes in cardiac output ranged from +3 to −3 per cent. In the 5 patients in whom left atrial systolic waves developed, changes in cardiac output ranged from +11 to +55 (mean +30 per cent) (Fig. 8). It is tempting to correlate the return of detectable atrial contraction with augmentation of the cardiac output. However, it is possible that the return of effective atrial systole may be delayed, and Braunwald has commented[7] that the beneficial effects of cardioversion may not be present immediately. The lack of information on atrial pressures in other studies may explain the variable conclusions reached about changes in cardiac output after cardioversion.

Hemodynamic changes after failure of cardioversion. Finally, it is of considerable interest to observe the hemodynamic changes in the 5 cases in which cardioversion failed. In only 1 such case (Case 2, Table III) were measurements of left ventricular end-diastolic pressures possible. The transient increase in mean left atrial pressure in this case must, in the absence of appreciable change in heart rate or cardiac output, indicate alteration in left ventricular function or distensibility. Furthermore, in 3 out of 4 cases of failure of cardioversion a transient increase in mean left atrial pressure occurred. The risk of pulmonary edema after successful cardioversion[19] has been assumed to be related to the return of effective left atrial systole. No such complication occurred during this study, but it is possible, on the basis of the mean left atrial pressures, that

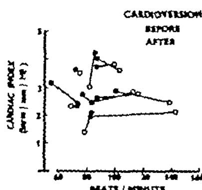


Fig. 7. Cardiac index and heart rate before and after successful cardioversion.

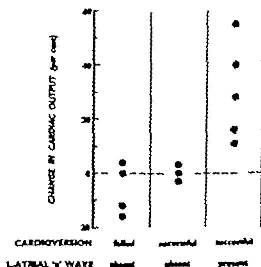


Fig. 8. Change in cardiac output after success and failure of cardioversion and in relation to the development of left atrial waves.



Fig. 9 Case No. 5 Left trial pressure tracings before ( ), immediately after (b), and 25 minutes after ( ) failure of cardioversion The pressure scale is I millimeters of mercury

there is a risk of pulmonary edema in the immediate post-shock period even when cardioversion has been unsuccessful (Fig 9) It is also clear (Fig 8) that the cardiac output sometimes falls after failure of cardioversion but it is possible that part of this fall in output is due to persistence of anesthetic effects After successful cardioversion the output was not significantly changed in cases in which no left atrial a wave developed and the tendency for the output to drop after failure of cardioversion may have been due to the greater electrical energy delivered to the myocardium in these cases a mean total energy of 400 joules was delivered in successful cases, as against 700 joules in unsuccessful cases.

Summary

The immediate hemodynamic changes occurring after D C cardioversion have been measured in 18 patients with rheumatic ischemic or thyrotoxic heart disease. Sinus rhythm was successfully restored in 13 patients.

Twelve out of 13 successfully cardioverted patients developed clearly visible right atrial a waves. Five out of 8 successfully cardioverted patients developed left atrial a waves. The lower incidence of return of effective atrial systole on the left side despite the return of normal atrial excitation is explained by the more severe left-sided disease.

Seven out of 12 successfully cardioverted patients had increased cardiac indices after cardioversion The other 5 patients showed either no change or minor falls. When discernible left atrial a waves returned after cardioversion appreciable increases in cardiac output occurred(range 11 to 55 per cent) When no discernible left atrial a wave returned changes in cardiac output were slight.

Significant reduction in cardiac output occurred in 2 out of 4 cases in which cardioversion failed In 3 out of 4 cases in which cardioversion failed a temporary increase in mean left atrial pressure occurred A similar temporary increase in left ventricular end-diastolic pressure occurred in the single case in which this was measured

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Late diastolic mitral regurgitation secondary to aortic regurgitation: Its relationship to the Austin Flint murmur

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The Austin Flint murmur is an apical diastolic rumble starting in mid or late diastole often noted in severe aortic regurgitation. Speculation as to the pathogenesis of this murmur has centered about vibrations produced during diastole by impingement of both the aortic regurgitant jet and the forward mitral valve flow on the anterior leaflet of the mitral valve. A recently noted feature of severe aortic regurgitation[1,2] is a clearly demonstrable reversal of the pressure gradient between the left atrium and ventricle in diastole, presumably leading to premature closure of the mitral valve. The occurrence of an Austin Flint murmur in association with such a reversed gradient would render inconsistent the older theories in regard to the pathogenesis of this murmur since forward flow from the left atrium to the left ventricle against this gradient would be unlikely. The present report concerns 3 patients with severe aortic regurgitation in whom a reversal of gradient during diastole and an Austin Flint murmur were present, and in whom a mild late diastolic mitral regurgitation was noted cineangiographically. In the light of this last mentioned finding, diastolic mitral regurgitation must be considered to be another possible cause of the Austin Flint murmur.

Methods and results

Complete details of history and physical examination were available in all 3 patients. Pertinent clinical, electrocardiographic, and roentgenographic features are outlined in Table I. Phonocardiograms were recorded using either a direct writing system, the Schwarzer Cardioscript ST4 (Fig. 1), or an Electronics for Medicine DR-8 photographic recorder (Fig. 2). The phonocardiographic findings were similar to the auscultatory findings listed in Table I. The prominent presystolic rumble at the mitral area lacked the crescendo character of the murmur of mitral stenosis. In one patient (Case 1) the phonocardiogram, pulmonary artery wedge pressure, and left ventricular pressure were recorded simultaneously during cardiac catheterization (Fig. 3). The time delay between

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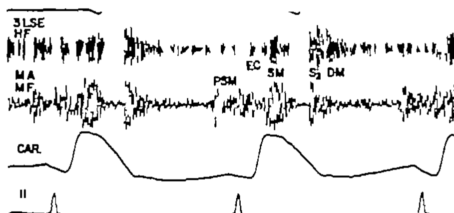


Fig. 1. Case 1. Phonocardiogram showing prominent apical presystolic rumble (*PSM*—Austin Flint murmur). Marker at top indicates 1 second. Letters: *3LSE*, Third left sternal edge. *MA*, Mitral area. *HF*, High frequency. *MF*, Medium frequency. *CAR*, Carotid pulse. *EC*, Ejection click. *SM*, Systolic murmur. *DM*, Diastolic murmur. S_2, Second heart sound. *II*, ECG Lead II. Described in Table I.

Table I. Clinical data

Case	*Age (yr.)*	*Etiology*	*Effort dyspnea*	*PND*	*Angina*	*Cardiac finding*	*ECG*	*Chest roentgenogram*
1 M.M. (NF)	43	Rh.H.D. SBE	+	0	+	Cardiomegaly; LV heave; S_1 diminished or absent; S_2 loud; ejection click all foci; ejection systolic murmur Grade 3/6 at base; long Grade 4/6 decrescendo diastolic murmur at base and LSE; Grade 2/6 presystolic rumble at apex	Sinus rhythm with LVH and digitalis effect	Enlarged LV; dilated thoracic aorta
2 G.M. (NF)	43	Unknown	+	+	+	Cardiomegaly; LV heave; S_1 diminished; occasional paradoxical split of S_2; ejection systolic murmur Grade 2/6 at base; long Grade 3/6 decrescendo diastolic murmur at base and LSE; Grade 2/6 presystolic rumble at apex	Sinus rhythm with intermittent pre-excitation; LVH and digitalis effect	Increased transverse diameter; definite enlarged LV
3 C.M. (NM)	52	Syphilitic	+	+	0	Cardiomegaly; LV heave; S_1 diminished or absent; S_2 physiologically split; ejection click all foci; ejection systolic murmur Grade 3/6 at base; long decrescendo diastolic murmur Grade 4/6 LSE as well as RSE; Grade 2/6 presystolic rumble at apex	Sinus rhythm with LVH and digitalis effects	Enlarged LV; dilated ascending aorta

NF, Negro female. *NM*, Negro male. *Rh.H.D.*, Rheumatic heart disease. *SBE*, Subacute bacterial endocarditis. *PND*, Paroxysmal nocturnal dyspnea. +, Present. 0, Absent. *LV*, Left ventricle. *LVH*, Left ventricular hypertrophy. S_1, First heart sound at apex. S_2, Second heart sound at upper left sternal edge. *LSE*, Left sternal edge. *RSE*, Right sternal edge.

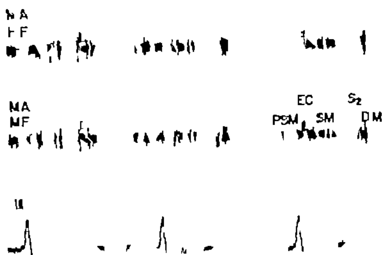


Fig 2. Case 3 Phonocardiogram showing typical presystolic rumble (Austin Flint murmur). Labeled as in Fig 1 Time lines 0 1 second. Described in Table I

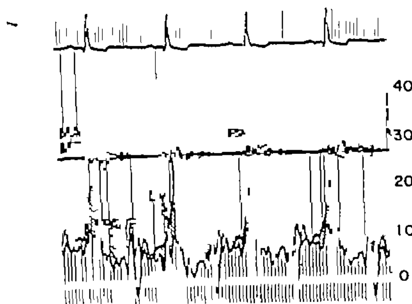


Fig 3 Case 1 Phonocardiogram (mitral area medium frequency) recorded simultaneously with left ventricular and pulmonary artery wedge pressures Pressure scale is in millimeters of mercury Time lines 0.04 second A presystolic murmur at the apex (*PSM*) occurs during the period of reversed atrioventricular pressure gradient (shaded area). *LV* Left ventricular pressure. *PAWP* Pulmonary artery wedge pressure. The pressure level recorded at this time were lower than those shown in Table II

phonocardiographic and pressure events was found to be negligible (0 016 second)

Right[11] and retrograde left heart catheterization[12] were simultaneously performed in each case The hemodynamic data (Table II) were obtained under steady state conditions. Cardiac output and cardiac index were determined by the indicator-dilution method and a pulmonary arteriovenous oxygen difference was simultaneously obtained. Cardiac Index was low only in Case 3 The zero reference level for the measurement of pressure was placed 5 cm. below the sternal angle All

Table II. Hemodynamic data

Case	BSA (M²)	Heart rate/min.	CI	Pulm ΔA–V O₂ (vol. %)	Pressures (mm. Hg): RA (Mean)	RV (S/D)	PA (S/Dm)
1	1.63	76	3.2	4.4	4	24/5	24/12 (18)
2	1.92	94	3.9	4.8	4	35/5	35/16 (24)
3	2.06	76	2.6	6.1	3	54/6	54/22 (32)

BSA: Body surface area. *CI*: Cardiac index, in liters/min./M² B.S.A. *Pulm ΔA-V O₂*: Pulmonary arteriovenous oxygen difference. wedge pressure. W: ve of left atrial contraction reflected in wedge pressure pulse. *S/Dm*: Systolic/diastolic (mean). *LV*: Left ventricle

pressures were measured through No. 7 catheters by means of strain-gauge manometers (Statham P23Db) and were recorded photographically (Electronics for Medicine DR-8). Sensitivity and reference levels of the pressure-measuring apparatus were matched prior to the simultaneous recording of pressures. Mean pressures were obtained by electronic damping. The pressures shown in Table II are the average of pressures obtained through two respiratory cycles. The difference in catheter delay of the right and left heart pressures was negligible (0.004 second).

The pulmonary artery wedge pressure pulse was used as a measure of left atrial pressure.[13] Criteria[14] for suitable wedge pressure curves were met. The wedge pressure pulses were phasic in form and were characterized by distinct *a* and *v* waves, with some superimposed catheter motion artifact. The elevation of pulmonary venous pressure noted in 2 of the cases along with little evidence of precapillary pulmonary hypertension are the circumstances in which the wedge pressure pulse reflects the left atrial pressure pulse with greatest fidelity.[15] Left atrial pressure events appearing in the wedge pressure pulse are delayed by about 0.02 to 0.08 second. This was taken into account in considering simultaneously obtained wedge and left ventricular pressures. The left ventricular end-diastolic pressure markedly exceeded the mean pulmonary artery wedge pressure in all cases (Table II) and also markedly exceeded peak *a* wave wedge pressure in 2 of the 3 patients (Cases 1 and 2). In all patients, left ventricular pressure exceeded pulmonary artery wedge pressure during much of the latter half of diastole. This is illustrated in Figs. 3 and 4. Atrial systole tended to diminish the negative gradient or possibly to reverse it transiently.

The duration of the period of left ventricular isovolumic contraction was measured as the time from the beginning of ventricular contraction to the point on the upstroke of ventricular systole corresponding in level to brachial arterial end diastolic pressure. Average values are listed in Table II along with the corresponding average cardiac cycle lengths. The elevated left ventricular end-diastolic pressures and relatively low arterial diastolic pressures are factors contributing to the brevity of this period as compared to the normal resting value of about 0.06 second.[1] This was particularly marked in Case 1 (Fig. 5).

Cineangiography with injections into the aortic root and left ventricle was performed in all cases. Forty to sixty cubic

	Pressures (mm Hg)						
	PAWP	*LV*					*LV isovolumic contraction period/R R cycle length (sec./sec.)*
	Mean	*Systolic*	*Early diastolic*	*End diastolic*	*Aorta (S/Dm)*	*BA (S/Dm)*	
16	8	155	1	28	165/58 (95)	155/45 (80)	0 025/0 90
22	17	140	6	32	133/70 (100)	148/70 (105)	0 030/0 65
24	20	175	7	30	175/80 (120)	182/82 (117)	0 035/0 80

simultaneously obtained with cardiac output *RA*, Right atrium. *RV* Right ventricle. *PA* Pulmonary artery *PAWP* Pulmonary artery
Early diastolic, Lowest left ventricular pressure. *End-diastolic* End-diastolic pressure of left ventricle.

centimeters of contrast material (Angio-Conray) was delivered in 2 to 3 seconds by a pressure injector (Cordis) Cineangiograms were recorded on 16-mm film exposed at 60 frames per second The degree of aortic regurgitation was severe in all instances by angiographic criteria since on injection into the aortic root the left ventricle opacified fully and to the extent of the ascending aorta within a few beats. Dilatation of the left ventricle was particularly apparent in Case 2 The left ventriculograms in Cases 1 and 3 and the aortogram in Case 2 were obtained in th right anterior oblique projection A mild but definite late diastolic or presystolic jet of mitral regurgitation was demonstrated in each case over several cardiac cycles, but none occurred during ventricular ejection. This phenomenon is diagrammed in Fig 6 since t was not well seen on reproductions of single cineangiographic frames. The time interval between the start of visible diastolic mitral regurgitation and th onset of ventricular ejection was assessed by singl framing and was found to be 0 20 0 15 and 0.20 second respectively aga nst average left ventricular isovolumic contraction periods of 0 025 0 030 and 0 035 second determined as described above. Relating this to the electrocardiograms recorded during angiocardiography (P R intervals of 0 20 0 20 and 0 18 second) places the onset of mitral regurgitation during or just following the P wave (Figs 4 and 6) and thus well before the beginning of ventricular systole. The Austin Flint murmur reversal of pressure gradient and mitral regurgitation were all present between the P wave and the onset of the QRS The electrocardiogram revealed no premature beats or other arrhythmia during cineangiography Pre-excitation was not present during cineangiocardiography in Case 2

Discussion

Since the Austin Flint murmur was first described in 1862 several mechanisms have been proposed to account for its genesis. [*] The majority of them assume a relative or functional stenosis of the mitral valve produced by the aortic regurgitant jet Herrmann [11] in 1926 noted that a lesion in the posterior cusp of the aortic valve could cause a regurgitant jet into the ventricle so directed as to displace the aortic leaflet of the mitral valve thereby causing it to encroach on the mitral orifice during diastole. Gouley [12] however found lesions mainly involving the right aortic leaflet in au led tients in whom an Austin Flint

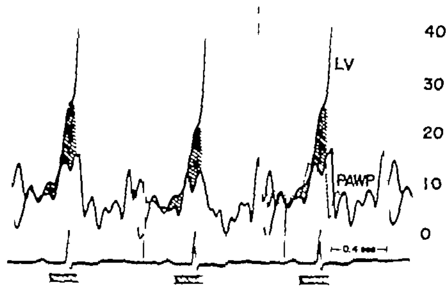


Fig. 4 Case 1 Simultaneous left ventricular and pulmonary artery wedge pressures. The pressure scale is in millimeters of mercury. Late diastolic reversal of the atrioventricular gradient is illustrated by shading. The dotted line indicates the approximate time delay when the wedge pressure is used as measure of left atrial pressure. The shaded blocks depict the period of diastolic mitral regurgitation as observed cineangiographically and related to the electrocardiogram. The dotted portion of each block indicates the period of left ventricular isovolumic contraction. It could not be determined with certainty whether the regurgitation extended into this phase of the cardiac cycle. *LV* Left ventricular pressure. *PAWP* Pulmonary artery wedge pressure. Further described in text.



Fig. 5 Case 1 Simultaneous left ventricular (*LV*) and brachial arterial (*BA*) pressure pulses. The pressure scale is in millimeters of mercury. The time lines are at 0.1-second intervals. The period of left ventricular isovolumic contraction is brief because of high ventricular end-diastolic pressure and low brachial arterial diastolic pressure. These pressures almost equalize at the end of compensatory pause (prior to the fourth BA pulse from the right). The following beat is an interpolated ventricular premature beat. Note that ventricular end-diastolic pressure is low prior to the next two postextrasystolic beats. The first of these is separated from atrial systole by a long P-R interval, and diastole is relatively short prior to each. Discussed in text.

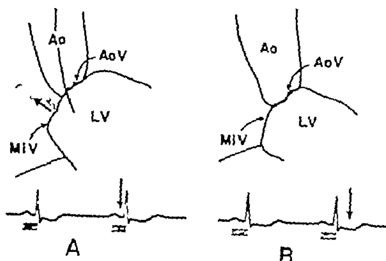


Fig. 6. Case 3. Sketch of frames from left ventriculogram, in right anterior oblique projection. A, At end diastole, there was faint mitral regurgitant jet. B, During mid-systole, the ventricle contracts and the aorta fills. The regurgitant jet is absent. The vertical arrows above the ECG indicate the timing of the two frames in the cardiac cycle. The shaded blocks below the ECG depict the period of diastolic mitral regurgitation as observed cineangiographically. A, Aorta; AV, Aortic valve; LV, Left ventricle; MV, Mitral valve.

present. He thought that the aortic valve regurgitant jet thus created could displace the lower portion of the anterior mitral curtain. On the other hand, it has been suggested by Turner (quoted by Phear[32]) and White[34] that dilatation of the left ventricle in these circumstances, if not associated with a change in circumference of the mitral valve ring, could cause relative mitral stenosis. The reversal of the pressure gradient across the mitral valve observed in the present cases during the period of the Austin Flint murmur makes explanations so far proposed inadequate to account for the genesis of the murmur. The coincidence of an Austin Flint murmur with a reversed pressure gradient and a late diastolic or presystolic mitral regurgitation suggests that these hemodynamic findings must play a part in the production of the murmur.

Marked reversal of the left atrioventricular pressure gradient in diastole has been previously reported. Wright and associates, in 1956 described the left ventricular pressure curve of a 16-year-old girl with aortic stenosis and severe aortic regurgitation. They found that left ventricular pressure exceeded left atrial pressure after mid-diastole. In 1957 Welch and associates[4] demonstrated experimentally in the dog that whenever aortic regurgitant flow exceeded resting cardiac output, left ventricular end-diastolic pressure exceeded mean left atrial pressure and reversed atrioventricular gradients were noted near the end of diastole. They concluded that there must be partial or complete closure of the mitral valve before ventricular systole in order to account for the paradoxical pressure gradient across the mitral valve. A similar assumption is reasonable in clinical cases such as the present and that possibility has been previously pointed out.[4, 20]

The validity of using wedge pressures instead of left atrial pressures as was done in this report might be questioned. The occurrence of mitral regurgitation during reversal of the left atrioventricular pressure gradient as demonstrated here is independent evidence that such a gradient does indeed exist, provided that the pertinent hemodynamics during angiocardiography are comparable to those during the recording of pressure. Left ventricular dynamics are undoubtedly affected by the forceful injection of large amounts

*Since the submission of this report, the reversed pressure gradient across the mitral valve was confirmed in case 1 during simultaneous transseptal and retrograde left heart catheterization.

of contrast material as in left ventriculography, however, artifactual diastolic mitral regurgitation must be exceedingly rare. Furthermore, in Case 2 diastolic mitral regurgitation was demonstrated by aortography on account of the large amount of contrast material washed back into the left ventricle in the aortic regurgitant flow, there being no catheter in the left heart. The elevation of left ventricular end-diastolic pressure responsible for the reversed pressure gradient across the mitral valve in these cases, is a function of heart rate, aortic regurgitant and mitral valve flow rates, and left ventricular compliance in diastole. A sharp elevation of left ventricular end-diastolic pressure may time well with atrial systole as in the present cases and in some illustrations from other reports.[6,30] Atrial systole could contribute to this sharp rise in left ventricular pressure by partially displacing the closed or nearly closed mitral valve cusps into the left ventricular cavity. A clue to the unlikelihood that the sharp rise in left ventricular pressure is due to atrial systole alone, and thus that the reversed pressure gradient in the present cases is false, due to failure of the wedge pressure pulse to reflect a larger "a" wave in the left atrial pulse, is seen in Fig. 5. Slight ventricular pulse irregularity initiated by an interpolated premature beat has shortened the second diastole from the right. A normally occurring P wave is not associated with the sharp rise in left ventricular pressure seen when the heart rate is regular, indicating that atrial systole is not the sole cause of this rise in pressure.

Several possible mechanisms can be suggested for the slight incompetence noted here of an apparently closed mitral valve. Dilatation of the mitral valve ring due to left ventricular enlargement could result in incomplete closure of the mitral orifice by the valve cusps. The valve-closing functions of early ventricular systole[17,2] would not be operative. Since this phenomenon occurs during the period of reduced ventricular filling, less momentum toward forward mitral valve flow would have to be overcome in initiating the regurgitation than would be the case earlier in diastole. Furthermore, the regurgitation could be exaggerated by atrial relaxation.

Although the possibility of diastolic mitral regurgitation in severe aortic insufficiency has been raised in the literature,[30]* its actual occurrence has not been described previously.

The term *Austin Flint murmur* is purely descriptive, having no definite connection with the mechanisms involved. The murmur in some instances could be due to the forward flow of blood through a relatively narrowed mitral valve, as previously suggested.[1,2,19-22,31,34] But in certain cases, such as the present ones, late diastolic or presystolic mitral regurgitation occurring in association with premature and incomplete closure of the mitral valve must be considered to be a likely cause.

Summary and conclusions

A unique finding in 3 cases of severe aortic regurgitation is described, namely, the cineangiographic observation of a late diastolic or presystolic mitral regurgitation associated with a reversal of the pressure gradient across the mitral valve and an Austin Flint murmur.

This reversed gradient, occurring after mid-diastole, tends to bring about premature closure of the mitral valve in these patients. However, this closure is apparently incomplete since a leak of blood from the ventricle to the atrium was demonstrated in late diastole or presystole. The possible mechanisms of this finding are discussed.

The occurrence of the Austin Flint murmur in these patients can be explained on the basis of diastolic mitral regurgitation.

We are grateful to Dr. Louis N. Katz for suggestions in preparing this report.

*This phenomenon has since been described by another group[30] independently after our report was submitted.

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Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment

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Since the demonstration of the antiarrhythmic properties of the new beta adrenergic blocking agent propranolol[1] several investigations have proved its efficiency in terminating paroxysmal atrial fibrillation.[2-4] In chronic atrial fibrillation slowing of the ventricular rate has been observed but the drug has not been deliberately used for conversion to sinus rhythm. In a preliminary communication we proposed that propranolol might act synergistically with quinidine. This was based on the observation that, in 2 patients in whom chronic atrial fibrillation had previously been converted to sinus rhythm only with large doses of quinidine pretreatment with propranolol permitted the use of small doses of quinidine to achieve sinus rhythm. Subsequently we tried to convert chronic atrial fibrillation to sinus rhythm with such combined treatment. The results are described below.

Material and methods

Eighteen trials of conversion in 17 patients with chronic atrial fibrillation are included in this study. The patients were selected from the consecutive material of our department, and only those with giant left atrium, severe heart failure or known sensitivity to quinidine or those over the age of 70 years were not subjected to a trial of conversion. There were 11 women and 6 men who ranged in age from 36 to 69 years. Eleven patients suffered from rheumatic heart disease with mitral valvular involvement, 5 patients had arteriosclerotic cardiovascular disease and in one patient no etiology could be determined. Detailed data on the patients are given in Table I. Digitalis medication was usually stopped when trial for conversion was decided upon. Anticoagulants were not given. Propranolol† 10 to 15 mg. was given in 3 or 4 divided oral doses for 2 to 4 days after which a ventricular rate of 65 to 80 was attained. At that time and while propranolol was continued oral quinidine was added in doses of 0.2 to 0.3 Gm. 3 to 4 times daily. The exact doses given until sinus rhythm was achieved are summarized in Table I. The trial was discontinued when sinus rhythm failed to appear after 5 days of the combined treatment.

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Table 1 Details of "combined" therapy in 17 patients

Patient	Sex	Age (yr)	Etiology	Duration of AF	Previous attempts at conversion	Propranolol pretreatment: Dose daily (mg)	Propranolol pretreatment: Number of days	Propranolol and quinidine: Dose daily (Gm) of quinidine	Propranolol and quinidine: Number of days	Success of conversion	Follow-up period (mo)
1 Y D	M	33	RHD	>10 y	2	80	11	0 6	1	Yes	9
2 H H	F	44	RHD	3 y	3	80	3	1 2	3	Yes	9
3 R.C	F	53	RHD	4 y	No	60	3	1 0	3	Yes	8
4 L D	M	42	RHD	>2 yr	1	40	3	0 8	3	Yes	8
5 C.M	F	36	RHD	Not know	No	40	4	1 0	3	Yes	8
6 T M	M	49	ASCVD	1	N	60	4	1 2	5	N	
7 S.Z	F	40	RHD	1 yr	3	40	4	0 8	3	Yes	
				1	4	40	4	0 8	4	Yes	
8. A S	F	38	RHD	2 yr	3	40	4	0 8	2	Yes	7
9 B.Z	M	44	Idiopathic	>3 yr	4	60	4	1 2	3	Yes	7
10 B R.	F	69	ASCVD	4 yr	1	80	4	1 0	5	No	–
11 P R	F	68	RHD	5 yr	1	40	3	0 8	3	Yes	Maintained for mo. oth
12 A R.	F	60	RHD	Not know	N	60	4	1 0	5	N	
13 O H	F	56	ASCVD	3 mo	N	30	3	0 6	2	Yes	5
14 A O	M	62	ASCVD	2	N	40	4	0 8	2	Yes	4
15. E.T	F	46	RHD	4 yr	3	40	4	0 8	2	Yes	4
16. T.F	F	63	ASCVD	Not know	N	40	3	0 8	3	Yes	4
17 A.T	M	43	RHD	>3 yr	N	40	4	1 0	4	Yes	3

RHD Rheumatic heart disease ASCVD Arteriosclerotic cardiovascular disease

Results

Eighteen trials of conversion of chronic atrial fibrillation in 17 patients were performed during this study. Fifteen trials ended with the appearance of sinus rhythm; in 3 patients this was not achieved. No trial was suspended because of side effects from one of the drugs. No embolic phenomena were observed. After the conversion all the patients were maintained on the combined treatment of the two drugs: the usual dose of propranolol was 30 mg and that of quinidine was 1 0 Gm daily. Sinus rhythm has been maintained in 13 patients for periods up to 8 months.

Comments

Previous investigators have used propranolol with success to terminate paroxysms of atrial fibrillation,[1-4] but apparently they did not try to convert chronic atrial fibrillation to sinus rhythm. The present study demonstrates that propranolol may act synergistically with quinidine and that this combination may be used efficiently to achieve sinus rhythm. This enhancing effect is not surprising in view of the many common effects of quinidine and propranolol, e.g., depression of myocardial contractility and decrease in blood pressure,[7-9] which point also to some common pathways of action of these drugs. Quinidine itself may also act as an adrenergic blocking agent, as suggested by Dreifus and co-workers. Angelakos and co-workers demonstrated a distinct alpha blocking effect of the drug, but beta blocking action could not be demonstrated. In view of these effects, Seaton's report[12] concerning the termination of quinidine-induced ventricular fibrillation with propranolol is rather surprising. However, critical review of this case report raises the possibility that the author might have been dealing with a digitalis-induced disturbance in rhythm; such arrhythmias are well known to respond extremely well to propranolol.

The decision to include all patients con

secutively in this study led us to try this treatment even in patients who would previously have been judged to be poor risk cases for conversion e g Patients 11 14 16 because of their advanced age and Patients 3 4 12 because of severe mitral valvular disease and marked hypertrophy of the left atrium It was satisfying to observe the appearance of sinus rhythm after small doses of both drugs without any side effects in these patients or in those who had needed large doses of quinidine sometimes up to toxic levels in previous attempts t nversion.

In all of the above-described patients after sinus rhythm had been achieved it was maintained by a combination of propranolol and quinidine In all but one patient (Patient 11) sinus rhythm has now been maint ined for 3 to 8 months. In 6 of the pat ent in this study sinus rhythm achieved at previous conversions had been maintained by quinidine treatment lone but relapses occurred 1 to 10 months after the conversion In one patient (Patient 7) who was maintained on quinidine and propranolol both drugs were withdrawn after 2 months because of gastrointest nal symptoms erroneously ttributed to one of the drugs used atrial fibrillation promptly recurred A new attempt at onversion was again successful and sinus rhythm is now once more well maintained Although the over all follow up period of 3 to 9 months is less than desirable for drawing conclusions it would appear that the combined maintenance treatment has merit This is not in agreement with the observation of Tsol kas and coworkers and Besterman and Friedlander[5] that propranolol alone has no value in maintaining sinus rhythm after electrical cardioversion Probably the more successful use in our study might be attributed to the combined use of propranolol and quinidine

Summary

A new method of drug treatment for the conversion of chronic atrial fibrillation to sinus rhythm is presented This consists of pretreatment with propranolol (Inderal) followed by the addition of small doses of quinidine Fighteen conversions were attempted by this method and in only 3 was sinus rhythm not obtained The successes included 5 patients who had previously required very large doses of quinidine alone in order to achieve sinus rhythm

The combination of propranolol and quinidine in small doses appears to be a simple safe and effective method for the achievement of sinus rhythm in patients with chronic atrial fibrillation

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Microcirculatory disturbances and human myocardial infarction

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Myocardial infarction without significant coronary lesions or acute occlusion in man has frequently been reported in the literature. Furthermore in many experimental studies an infarctoid cardiopathy, namely a myocardial coagulative necrosis, has been obtained. Recently the low incidence of acute occlusion in the human infarct has been emphasized [?] and evidence has shown that in most of the human cases the cardiac infarct is not a true infarct according to the general meaning of the term. It has been estimated that in more than 90 per cent of these cases only the ambiguous term "myocardial infarction with acute occlusion" applies. Therefore the different theories that have been proposed for "idiopathic myocardial coagulative necrosis" take on a particular significance. Among these theories the most widely debated are those of acute or chronic coronary insufficiency of intracardiac or extracardiac origin,[10] coronary spasm,[11] intramural arterial lesions,[12] metabolic disturbances by catecholamines,[13] and settling of blood cell masses.[14]

This paper concerns the relationship of the myocardial alterations to the occlusive lesions of the small intramyocardial branches. These lesions are numerous and widely disseminated in the hearts of patients who died from Moschcowitz's disease. Usually referred to as "thrombotic thrombocytopenic purpura" (TTP), this disease is characterized, according to Singer and Bornstein, by purpura, bleeding disorders, thrombocytopenia, severe hemolytic anemia, intermittent mental and neurologic disturbances, and myriads of platelet thrombi in the small arterioles and capillaries of almost all of the organs of the body. TTP offers a unique opportunity in human pathology to evaluate the above-mentioned relationship since the widespread dissemination of vascular lesions has its highest incidence in the heart.

Methods

Thirty-nine cases of thrombotic thrombocytopenic purpura collected from the files of the Armed Forces Institute of Pathology were studied. The files of the AFIP include case material from the military, Veterans Administration, and civilian sources. In each case the clinical and autopsy records, block, wet tissue, and slides of all the main organs were available. Twenty-four cases were male and 15 were female. The age range was

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from 21 to 72 years in the men averaging 36.1 years and from 21 to 59 years, averaging 38 years in the women.

All of the main organs in these 39 cases were histologically examined and the slides of each specimen were stained by hematoxylin and eosin, Movat periodic acid Schiff (PAS), Mallory's phosphotungstic acid-hematoxylin, Luna's canaliculi stain, and Rinehart-Abul Haj stain for acid mucopolysaccharides. In 3 cases, hematoxylin-eosin stained serial sections of two specimens from the right and left cardiac ventricular walls were studied. The frequency of the vascular lesions in each single slide has been evaluated as follows: 0 – no lesion found; 1+ – less than 5 lesions; 2+ – between 5 and 15 lesions; 3+ – more than 15 lesions.

Results

A complete discussion of TTP based on our own cases as well as on a review of 220 cases from the literature will be published in the near future. In this paper, however, we are concerned only with the obstructive or severely stenotic lesions of the arteriolar precapillary intramural branches of the myocardium and the related myocardial damage. These vascular lesions were present in all of the hearts examined with a frequency that was evaluated as 1+ in 3 per cent of cases, 2+ in 37 per cent, and 3+ in 60 per cent. The vascular lesions were not limited in location to any particular area of the heart but were disseminated throughout, chiefly involving the arterioles. The occlusive material is strongly PAS positive, even after digestion, showing little if any affinity for the collagen or acid mucopolysaccharide stains. In most of the cases it is possible to demonstrate an endothelial surface and very frequently endothelium-like cells appear within the abnormal material. More rarely there is a similar more granular material on the endothelial surface of the obstructive neoformation. Frequently the vessels appear to be highly dilated, showing a pattern resembling recanalization or glomeruli.

In 29 cases (74.3 per cent) a focal myocarditis was present, consisting mainly of mild polymorphonuclear infiltration without damage to the myocardial cells. Focal hemorrhages were found in 31 cases (79.5 per cent) and edema only was demonstrated in 20 cases (52.6 per cent). In only 4 cases (10.2 per cent) were rare, small foci of early coagulative necrosis present, without cellular reaction and apparently without any relationship to occluded arterioles. In 2 of these cases the right ventricle was involved and in the other 2 the left ventricle. In 12 cases (31.5 per cent) scant, small foci of myocytolysis were found. Three out of 4 cases with focal early coagulative necrosis also showed myocytolysis. The terminal episodes in the 4 cases with focal early coagulative necrosis were coma in 3 and sudden death in 1. In all of the cases with focal myocytolysis the terminal episode was coma, with the exception of 2 cases in which death was due to shock after splenectomy.

Conclusions

Acute focal myocardial necrosis has been reported in 33.3 per cent of 159 cases reviewed in the literature. Furthermore, most of these authors emphasized the disproportion between the limited extension of the necrotic damage and the diffuse dissemination of severe vascular lesions. In our material, however, the occurrence of extremely rare minimal foci of coagulative necrosis of the myocardium was found in only 10.2 per cent of the cases. In none of these cases was there a direct relationship between the site of the vascular lesion and the location of the myocardial damage as shown by serial sections; widespread dissemination of the vascular obstruction was maximal (Figs. 1-3).

Other myocardial alterations found, such as myocarditis, focal hemorrhage, focal myocytolysis, and edema, have no relationship to the coagulative necrosis typical of the myocardial infarct and therefore they will not be considered in the present discussion.

The finding of occasional focal coagulative necrosis of the myocardium in cases of TTP does not support the hypothesis that the obstructive involvement of the intramyocardial branches, even though extensive, may be the cause of the myocardial infarction in the absence of an effective acute occlusion of a main extramural branch. On the contrary, evidence

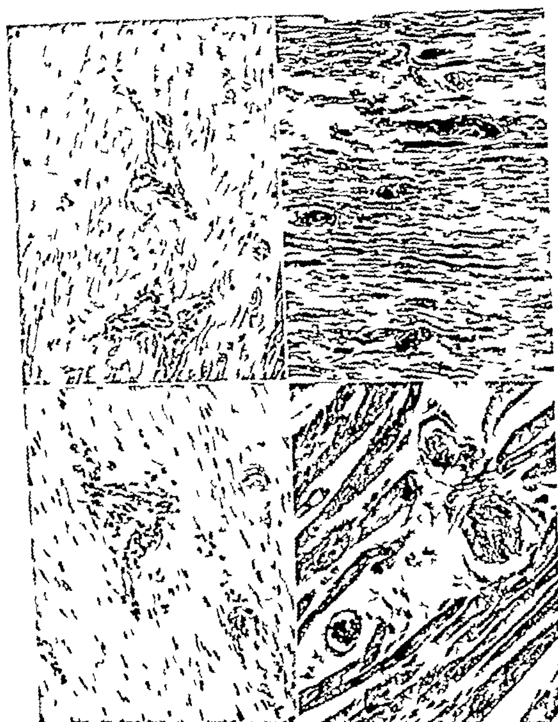


Fig. 1. Some patterns of thrombotic thrombocytopenic purpura in the myocardium and stenotic and occlusive lesions of the intramyocardial branches without myocardial damage. *Upper left.* From 33-year-old female Caucasian patient. Hematoxylin-eosin, ×165. AFIP Neg. 65-4320. *Upper right.* From 25-year-old female Caucasian patient. Periodic acid-Schiff ×115. AFIP Neg. 65-4240. *Lower left.* From 15-year-old male Caucasian patient. Hematoxylin-eosin, ×210. AFIP Neg. 65-4340. *Lower right.* From 33-year-old female Caucasian patient. Hematoxylin-eosin, ×350. AFIP Neg. 65-4332.

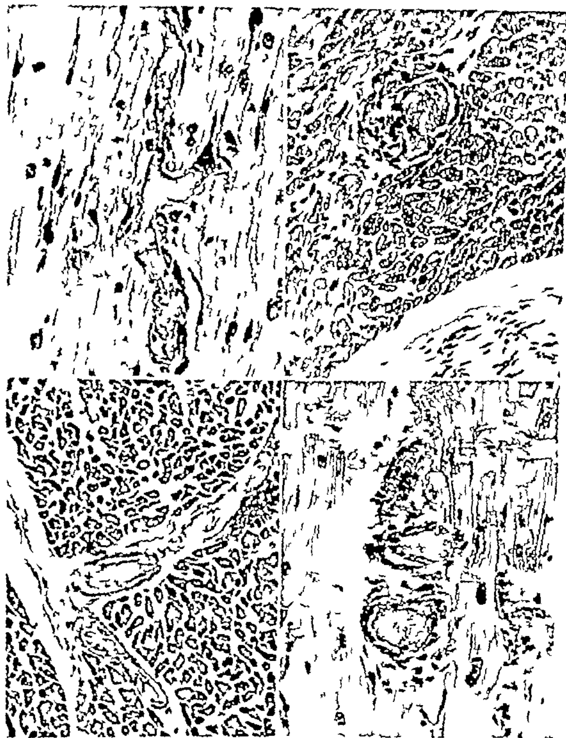


Fig. 2. *Upper left*: From 33-year-old female Caucasian patient. Periodic acid-Schiff. ×530. AFIP Neg. 65-4476. *Upper right*: From 23-year-old male Caucasian patient. Hematoxylin-eosin. ×165. AFIP Neg. 65-4449. *Lower left*: From 33-year-old male Negro patient. Hematoxylin-eosin. ×180. AFIP Neg. 65-4480. *Lower right*: From 33-year-old female Caucasian patient. Hematoxylin-eosin. ×550. AFIP Neg. 65-4471.

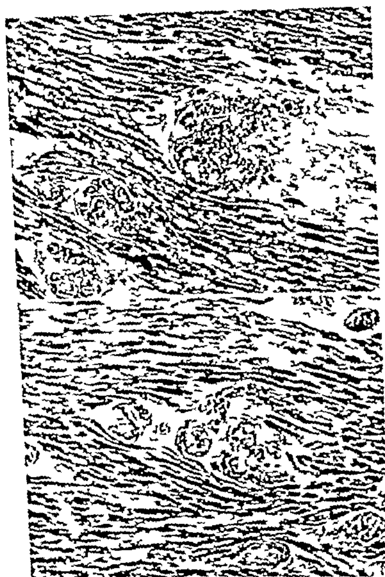


Fig. 3. *Upper.* From 25-year-old female Caucasian patient. Hematoxylin-eosin, ×100. AFIP Neg. 65-4264. *Lower.* From 23-year-old female Caucasian patient. Hematoxylin-eosin, ×130. AFIP Neg. 65-4265.

exists that the normal anastomotic circulation is capable of compensating efficiently for this type of widespread involvement.

TTP is, in most instances, a short term disease. 82 per cent of the patients reported on in the literature and 90 per cent of our own patients died within 35 days from the onset of the first symptoms and signs (42 and 52 per cent, respectively, with n 14 days; 21 and 20 per cent, respectively, within 7 days). In view of the histologic pattern, it is difficult to evaluate the exact age of the obstructive lesion, the nature of which is still debated. Among the characteristic histologic features of this lesion are the absence of connective or reticular tissue, the absence of or only minimal inflammatory reaction, the apparent proliferation of the endothelial cell (which in most of the lesions covers the collected fibrinoid-like material and sometimes seems to penetrate into it) and deposits of generally granular material superimposed on the more compact endothelium-lined nodules. The usually short course of this disease and the apparent

endothelial proliferation would support the concept that the vascular lesions are definable as acute and recent in most cases. These vascular lesions are still old enough however to have produced myocardial necrosis if a direct relationship exists between them since it has been well established by routine histologic procedures that after its onset the myocardial infarction cannot be demonstrated earlier than 8 to 12 hours. On the basis of our study we conclude that the acute recent occlusions of the intramyocardial artery do not induce myocardial coagulative necrosis

Summary

Thirt nine cases of thrombotic thrombocytopenic purpura (Moschcowitz s disease) were examined and the severe obstru ti e in olvement of the intramyocardial arterial branches was compared to the myoc rdial condition In only 4 cases (10 2 per cent) was an occ sional microfocal coagulati e necrosis present despite the massi e involvement of the intramural branches The conclusion therefore is that the obstructive lesions of the intramyocardial arterial portion cannot be the cause of the so-called myocardial infarction without acute occlusion of the main extramural branches

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The electrocardiographic recognition of left atrial enlargement in childhood

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It is generally acknowledged that left atrial enlargement often cannot be recognized on the basis of conventional electrocardiographic criteria. Electrocardiographic measures of left atrial enlargement or abnormality, such as increased P wave duration or voltage, leftward deviation of the frontal P axis, and changes in configuration of the P wave, have been found to be lacking in either specificity or sensitivity or both. Attempts to increase sensitivity, such as use of the P:P-R segment ratio, have in turn resulted in an unacceptable number of false positive diagnoses.

More recently, the use of right-sided precordial leads has been advocated for the assessment of left atrial enlargement, and prominent negativity of the terminal portion of the P wave in Lead V has been equated with left atrial abnormality. Because evaluation of the left atrium by analysis of the P wave in Lead V has not been reported in the pediatric age group, the present study was undertaken. Normal standards for configuration and measurement of the terminal portion of the P wave in this lead are derived. These values are then applied, along with conventional electrocardiographic measures of left atrial abnormality, to a group of infants and children with known left atrial overload. Electrocardiographic and x-ray diagnosis of left atriomegaly are then compared.

Materials and methods

Electrocardiograms were obtained on two groups of infants and children. Group I was comprised of 145 individuals who had no evidence of cardiovascular disease. Group II was comprised of 51 patients who had varying degrees of left atrial volume overload.

Group I (control) is subdivided by age into five categories, A—E. One hundred ninety-nine tracings were obtained from the 145 individuals in Group I; in some instances there were serial tracings on the same subject. In Group I-A are 50 normal premature infants, each less than 24 hours of age. These babies were followed until discharge and at no time did they show evidence of illness. Similarly, Group I-B is made up of 72 normal full-term babies 1-3 days of age. Group I-C consists of 26 normal premature infants, each 4 weeks of age, and in Group I-D there are 50 infants born prematurely on whom tracings were made at age 9-12 months. Finally, Group I-E is comprised of 51 other children who

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ranged in age from 4 to 12 years. These children were patients admitted to our pediatric surgery wards; none had evidence of cardiovascular disease.

Group II (abnormal)—ages 3 months to 12 years—is divided into 22 patients (Group II A) who had ventricular septal defect with left-to-right shunt and 29 patients (Group II B) who had mitral regurgitation. The diagnosis of ventricular septal defect was confirmed by cardiac catheterization in the 22 patients with this lesion. In none did the right ventricular systolic pressure exceed 50 mm. Hg nor was the end-diastolic right ventricular pressure abnormally elevated. On this basis none of these 22 patients is considered to have an appreciably increased right atrial work load which might alter the P vector. The pulmonary-to-systemic flow ratio ranged from 1.0 (in which cases a definite shunt was not detected by oxygen saturation measurements) to 6.4 with an average ratio of 2.0. Four of these patients with ventricular septal defect had an associated lesion: mild infundibular pulmonic stenosis and a small patent ductus arteriosus in 1 each and aortic regurgitation in 2 others.

Of the 29 patients with mitral regurgitation in Group II B, 21 had rheumatic heart disease. None of these underwent cardiac catheterization. In all there was a well-localized apical systolic murmur and all had other typical clinical and laboratory features of acute rheumatic fever at one time or another in their course. Of these 21, 7 had electrocardiograms recorded during an acute phase of rheumatic activity. Tracings in the remainder were obtained after all clinical and laboratory evidence of acute rheumatic fever had subsided. Four of the 21 had associated aortic regurgitation and in 6 there was congestive cardiac failure.

Eight of the 29 patients in Group II B had nonrheumatic mitral regurgitation. Right-sided and left-sided cardiac catheterization was performed in 6. Insufficiency of the mitral valve in these 8 children was either congenital, secondary to bacterial endocarditis, or associated with Marfan's disease or endocardial fibroelastosis. Two of the 3 with congenital mitral regurgitation had associated coarctation of the aorta and one of these had a patent ductus arteriosus also. None had an atrial septal defect.

Twelve-lead direct-writer recordings were obtained by experienced technicians at a paper speed of 25 mm. per second and a voltage standardization of 1 mm. per millivolt. All tracings were examined and measurements made using a 10X magnifying lens. Amplitude was estimated to the nearest 0.25 mm. and duration to the nearest 0.01 sec. Any abnormality in configuration of the P wave in the standard leads was noted and the P wave duration, P-R interval, and P-R segment were measured in either Lead I or Lead II. The precordial leads were also analyzed for abnormality in P wave morphology. In Lead V_1 the configuration of the P wave was observed and if it was diphasic or negative an average measurement of both amplitude and duration of the negative component was obtained. Measurement of the negative P V_1 was made according to Fig. 1. If the terminal portion of the P wave in Lead V_1 showed just minimally discernible negativity, it was arbitrarily considered to be equal to 0.25-mm. amplitude and .01-sec. duration. Attention is called to the fact that only the negative portion of the P wave in V_1 was considered in making these terminal measurements. This is in contrast to the study of Morris and associates, in which the terminal positive deflection as well as the negative deflection were measured. The terminal positive P deflection is ignored in the present study because quite frequently no notch was found indicating the onset of inscription of the terminal or left atrial portion of a monophasic positive P wave. The product of terminal negative amplitude and duration of the P wave in Lead V_1 is used to provide an area-estimate of left atrial depolarization. This product is termed the "terminal P V_1 index."

In establishing normal standards for P wave measurements the 90th percentile has been arbitrarily selected as the upper limit of normal.[1] It is thought to be preferable to utilize such a percentile value in analysis of the measurement data since distribution was not found to be normal but skewed toward the right. The chi square method with Yates correction was used to estimate probability in certain comparisons.

Results

Group I Normal values In Table I are data in the normal group relating to P wave morphology in Leads V and V_1. Sixty-one per cent of the combined group have a d phasic + − wave in Lead V. The variation of from 43 to 74 per cent in incidence of diphasic contour among the subgroups is not significant (p < 50) Considerable variation (13 to 64 per cent) has been reported in the incidence of diphasic P V_1 in adults [11,12] with the most recent estimate being 64 per cent. A diphasic P wave is infrequently found in Lead V in any childhood age group.

It is seen in Table I that when P V_1 is diphasic only very infrequently is the terminal negative deflection either equal to or greater than the initial positive component. In only per cent of the entire group is the negative deflection greater than the positive.

Measurement of the terminal negative P deflection in V_1 is summarized in Table II. Comparison of voltage duration and index measurements in the different age groups reveals no appreciable or consistent variation in any of these measurements related to age. The p values are not significant at the 5 per cent level even when only the extreme Groups I A and I E are compared. Considering the index there is no variation except in the third decimal place in any age group for the average 50th percentile or 90th percentile values. On the basis of these data there is little significant or measurable difference in magnitude of

Terminal P Duration X Terminal P Amplitude
Terminal P Index

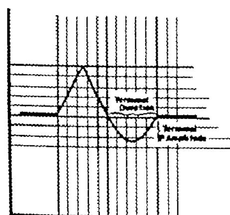


Fig. 1 Measurement of the terminal P V index. A diphasic (+/− P) wave in Lead V is diagrammed and the method of measuring the terminal negative deflection is indicated.

Table I P wave morphology Group I (control) in Leads V and V

Age group	P wave in Lead V (%)		Diphasic P wave in Lead V (%)			P wave Lead V (%)	
	+	+/−	> <	= =	</>	+	+/−
I A Prematures 24 hr	26	74	89	3	8	88	12
I B Full-term 1 3 days	55	45	90	0	10	86	14
I-C Infants 1 mo.	38	62	63	25	12	—	—
I D Infants 9-12 mo.	28	72	83	14	3	—	—
I E Children 4-1 y	57	43	98	0	2	100	0
All age groups	39	61	85	8	7	93	7

*One individual with completely negative P wave in Lead V.
+ Monophasic positive P wave +/− Diphasic P wave > < Positive component greater than negative component. = = Positive and negative components equal. </> Negative component greater than positive component.

Table II P V₁ measurements for Group I (control)

Group I (control)	Number of patients	Age	Terminal P duration (sec)	Terminal P amplitude (mm)	Terminal P index (mm sec)	
I A			0 02	0 39	0 008	Av
Premature newborn	50	<24 hr	0 01	0 25	0 005	50%
	(37)		0 03	0 75	0 015	90%
			0 03	1 50	0 030	Max.
I B			0 02	0 45	0 011	Av
Full-term newborn	22	1-3 days	0 02	0 50	0 005	50%
	(10)		0 035	0 50	0 015	90%
			0 035	1 0	0 035	Max.
I-C			0 02	0 36	0 007	A
Infants	26	1 mo.	0 01	0 25	0 005	50%
	(16)		0 03	0 50	0 015	90%
			0 03	0 75	0 020	Max.
I D			0 02	0 27	0 007	Av
Infants	50	9-12 mo.	0 02	0 25	0 005	50%
	(36)		0 03	0 25	0 008	90%
			0 04	0 50	0 030	Max.
I E			0 025	0 32	0 011	Av
Children	51	4-12 yr	0 02	0 25	0 005	50%
	(23)		0 04	0 25	0 010	90%
			0 08	1 25	0 100	Max
			0 02	0 36	0 009	A
All age groups	199	Birth to	0 02	0 25	0 005	50%
	(122)	12 yr	0 03	0 50	0 015	90%
			0 08	1 50	0 100	Max.

Numbers in parentheses indicate number of patients in each age group with diphasic, +/− P-wave configuration in Lead V₁. The average, 50th percentile, 90th percentile, and maximal values for the terminal P V₁ deflections are given.

the terminal negative P deflection in Lead V₁ from birth through 12 years of age in routine recordings. The 90th percentile measurements for the entire normal group are terminal P V₁ duration 0 03 sec., terminal P V₁ voltage 0 50 mm and terminal P V₁ index, 0 015 mm sec (The respective 95th percentiles are 0 04 sec 0 75 mm and 0 02 mm sec)

In Table III results of analysis in Groups I D and I E of P wave duration and P/P R segment ratio (in the standard leads) are presented The *upper limit of normal* P duration in 9—12 month infants and in 4—12 year children is quite similar In the combined group the 90th percentile for P duration equals 08 sec. This figure coincides with previously published data[1,4] In 42 per cent of the combined group the P/P R segment ratio is greater than 1 6 the value considered to be the upper limit of normal in children as well as in adults.[8]

In less than 10 per cent of the entire normal population is there either flattening or notching of the P wave in Leads I II V₅ or V₆. When notching is present normally the interval between the peaks does not exceed 0 03 sec.

Group II Abnormal values As seen in Table IV 82 per cent of all patients with left atrial overload have a diphasic +/− P wave in Lead V₁ This configuration occurs *in only 61 per cent of our normal subjects* (p < 01) Twenty two per cent of the patients with left atrial overload have a diphasic P wave in Lead V₁ in comparison with only 7 per cent of normal controls (p < 03) In one third of the patient group with diphasic P V₁ configuration the negative component is more prominent

Table III. Ninetieth percentile and maximum values for P wave duration and P/P R segment ration in Standard Leads I or II (Subgroups I D and I E only)

Age group	P-wave duration in Lead I or II		P/P R segment ratio		
	90%	Max	90%	M	> 1.6
I D Infants 9-12 mo.	0.08	0.10	2.0	3.0	45%
I E Children 4-12 y	0.09	0.10	2.0	4.0	39%
Combined groups (I D and I E)	0.08	0.10	2.0	4.0	42%

Table IV. P wave morphology in Group II (abnormal) is compared with that in Group I (control)

Group	P wave in Lead V (%)		Diphasic P wave in Lead V (%)			P wave in Lead V (%)	
	+	+/−	>/<	=/=	</>	+	+/−
Group I (control)	39	61	85	8	7	93	7
Group II A‡	18	82	67	5	29	86	14
Group II B‡	17	83†	54	8	38	72	28
Group II (abnormal)	18	82	60	7	33	78	22

*One patient with monophasic negative P V.
†Two patients with monophasic negative P V.
‡Group II-A and II-B refer to patients with ventricular septal defect and mitral regurgitation, respectively. The [illegible] the same indication as in Table I.

than the positive in only 7 per cent of normal subjects is this the case ($p < .01$).

Measurements of the negative P V_1 in Group I and Group II are compared in Table V. Since there is no statistical difference ($p > .10$ for all measurements) between Groups II A and II B they shall be considered together. The average terminal P V duration and amplitude in the total patient group are each twice those in the control group. The average terminal P V index is almost four times that of the normal group. Examples of tracings with abnormal negative P deflection are seen in Fig. 2. Only 7 per cent of the normal group have a terminal P V_1 index greater than 0.015 whereas this is the case in 41 percent of the patients with left atrial overload (see Fig. 3). These differences are statistically significant ($p < .01$).

In consideration of why only 41 per cent of the patients with known left atrial overload have posterior displacement of the terminal P vector the 51 patients in Group II were subdivided into two groups—one with "mild" and the other with "prominent" left atrial overload on the basis of other electrocardiographic and x-ray criteria. Twenty-one of these 51 patients had neither left ventricular hypertrophy by electrocardiogram nor cardiac or left atrial enlargement by roentgenogram and were designated the "Mild Left Atrial Overload" group. Thirteen of the 51 patients had a combination of left ventricular hypertrophy by electrocardiogram and also x-ray evidence of both cardiac and left atrial enlargement. These were placed in the "Prominent Left Atrial Overload" group. Results appear in Table VI. Ninety-tw

Table V P V₁ measurements in Group II (abnormal) compared with those in Group I (control)

Group	P V₁ term l d rat on				P V₁ terminal voltage				P V₁ terminal index			
	1	50%	90%	Max	Av	50%	90%	Max	Av	50%	90%	Max.
Total Group I (co trol)	0 02	0 02	0 03	0 08	0 36	0 25	0 5	1 5	0 009	0 005	0 015	0 100
Group II A	0 04	0 04	0 06	0 06	0 50	0 25	1 0	1 5	0 022	0 010	0 040	0 090
Group II B	0 04	0 05	0 06	0 07	0 82	0 38	1 6	3 0	0 042	0 020	0 120	0 210
Total Group II (abnormal)	0 04	0 04	0 06	0 07	0 80	0 25	1 5	3 0	0 034	0 010	0 100	0 210

Groups II A and II-B refer patient h ventricular septal defect and mitral regurgitation, respectively

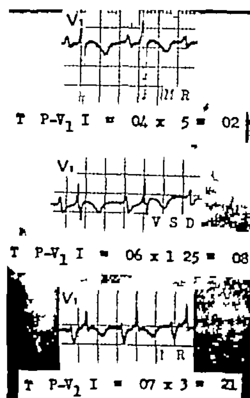


Fig 2 Represent ti examples of electroc rdiographic tracings show ng abnormal negativit of the P w in Le d V T P V I Term nal P V Index *M.R.* M tral regurgit tion. V S D Vent icular septal defect

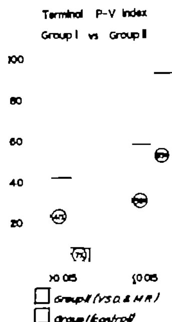


Fig 3 The terminal P V Index i Group I (control) ersu Group II (bnormal). The scale on the ordinat indicates per cent. *M.R* Mitral regurgitation *V S.D* Ventricular septal defect.

per cent of those with prominent left atrial overload have an abnormal terminal P V index whereas only 10 per cent of the group with mild overload have abnormal negativity of P V₁ (p < 01) Only 11 per cent of those patients with ventricular septal defect with a pulmonary to-systemic flow ratio less than 1.5 have a terminal P V index > 0 015 whereas 54 per cent of those with a pulmonary to-systemic flow ratio greater than 1.5 have an abnormal terminal P V₁ index (p < 11) On the basis of these comparisons it appears that negativity of the P wave in Lead V₁ is directly related to the degree of left atrial overload

Next an attempt was made to separately

Table VI. Per cent of patients with abnormal P V terminal index among those with mild and those with prominent left atrial overload (see text)

Patient group	Mild left atrial overload			Prominent left atrial overload		
	Number	Per cent with P V index > 015	A Qp/Q	Number	Per cent with P V index > 015	A Q Q
V.S.D.	9	11	1 3	5	80	3 4
M.R.	12	8	—	8	100	—
Total	21	10	—	13	9	—

V.S.D. Ventricular septal defect. M.R. Mitral regurgitation. A Q Q Average pulmonary-to-systemic flow ratio.

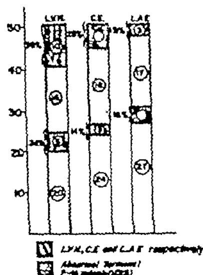


Fig. 4. Comparison in Group II of abnormal terminal P V index with presence of left ventricular hypertrophy (L.V.H.), cardiac enlargement (C.E.) and left atrial enlargement (L.A.E.). V.S.D. Ventricular septal defect. M.R. Mitral regurgitation. The scale on the ordinate refers to number of patients, as do the encircled numbers.

correlate abnormality of the terminal P V index with left ventricular hypertrophy, cardiac enlargement, and left atrial enlargement, respectively. Reference to Fig. 4 reveals that negative deflection of the P wave in Lead V correlates quite well with radiographic enlargement of the left atrium—enlargement of the left atrium by x-ray evidence was diagnosed in this study only when both the anterior and posterior walls of the barium filled esophagus were displaced. Seventeen (81 per cent) of the 21 patients with an abnormal terminal P V_1 index had left atrial enlargement by x-ray study. Cardiomegaly also correlates quite well with the presence of an unusually prominent negative component of the P wave in Lead V. Terminal P V abnormality correlates least well with electrocardiographically diagnosed left ventricular hypertrophy. Although 76 per cent of patients with an abnormal P V index had left ventricular hypertrophy, 38 per cent of those with left ventricular hypertrophy had a normal P wave in Lead V.

How the terminal P V_1 index compares with conventional electrocardiographic measures of left atrial abnormality is diagrammed in Fig. 5. In 41 per cent of the patients of Group II left atrial abnormality can be diagnosed on the basis of a terminal P V index > 0.015 mm. sec. Fifty-three per cent have left atrial abnormality on the basis of prolongation of the P wave in Leads I or II beyond .08 sec. Prolonged P duration may identify left atrial abnormality somewhat more frequently than does an abnormal terminal P V index but the difference between these two parameters is not statistically significant (p > .25). Although 51 per cent of the patients have an increased P:PR segment ratio, this ratio is similarly increased in 42 per cent of normal subjects. Abnormal P wave morphology such as notching or flattening

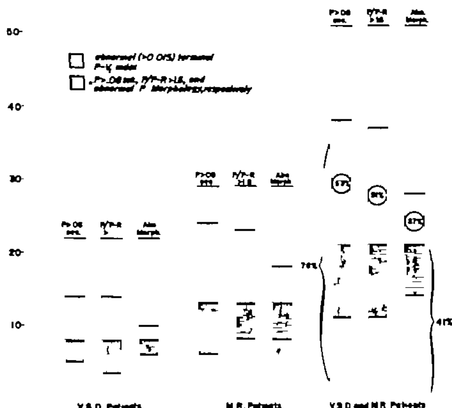


Fig 5 Comparison of four separate indices or measures of left atrial abnormality Abbreviations and notation as in Fig 4 Encircled percentages refer to the frequency with which each measure indicates left atrial abnormality in Group II

is found in only 27 per cent (14 patients) Of these 7 also have an abnormal P V_1 index and all but one have prolonged P wave duration

If a combination of abnormal P V index and prolongation of the P wave is employed (see Fig 5) left atrial abnormality can be diagnosed in 75 per cent of the patients in Group II Among the remainder who have neither P wave prolongation nor a terminal P V_1 index > 0 015 mm sec only 8 per cent have left atrial enlargement by x ray evidence and only 15 per cent have cardiomegaly

The various electrocardiographic parameters of left atrial abnormality were next compared after dividing the patients in Group II as before into those with mild and those with more severe left atrial overload The results of this comparison are shown in Table VII Abnormal terminal P V_1 index and abnormal P wave morphology indicate left atrial abnormality only in patients with more significant degrees of left atrial overload In this group an abnormal P V_1 terminal index is present in 92 per cent whereas abnormal P wave morphology is present in only 43 per cent ($p < .09$) P wave prolongation and P/P R segment ratio correlate poorly with the degree of left atrial overload ($p < .50$ and $< .20$ respectively) and detect left atrial abnormality equally unsuccessfully in both mild and prominent overload groups.

In Table VIII the electrocardiographic measures of left atrial abnormality are related to radiologic evidence of increased atrial size. Eighty-five per cent of the

*Table VII. Electrocardiographic measures of left atrial abnormality compared in patients with mild and in those with prominent left atrial overload**

Patient group	*Number*	*P V1 index >0.035 (%)*	*P wave > 0.08 sec (%)*	*P/P R segment >1.6 (%)*	*Abnormal P morphology (%)*
Mild Left Atrial Overload					
V.S.D.	9	11	33	33	0
M.R.	12	8	58	42	17
Total	21	10	48	38	10
Prominent Left Atrial Overload					
V.S.D.	5	80	40	80	20
M.R.	8	100	67	44	56
Total	13	92	57	57	43

*Prominent left atrial overload: Left ventricular hypertrophy by ECG and cardiomegaly and left atriomegaly by x-ray findings. Mild left atrial overload: None of the aforementioned criteria.

Table VIII. Electrocardiographic measures of left atrial abnormality compared in patients with radiographically enlarged left atrium and in those with no x-ray evidence of left atrial enlargement

Patient group	Left atrial enlargement by x-ray				No left atrial enlargement by x-ray			
	P V1 > 0.035 (%)	*P > 0.08 sec (%)*	*P/P R segment >1.6 (%)*	*Abnormal P morphology (%)*	*P V1 > 0.035 (%)*	*P > 0.08 sec (%)*	*P/P R segment >1.6 (%)*	*Abnormal P morphology (%)*
V.S.D.	67	56	78	22	15	31	31	8
M.R.	100	64	36	45	9	50	50	18
Total	85	60	55	35	11	43	43	14

V.S.D.: Ventricular septal defect. M.R.: Mitral regurgitation.

patients in Group II with an enlarged left atrium by x-ray study have an abnormal P V1 terminal index ($p < 0.01$) whereas P wave prolongation and abnormal P contour are present in only 60 per cent and 35 per cent, respectively. Only 11 per cent of the patients with no roentgenographic enlargement of the left atrium have an abnormal terminal P V1 index.

Discussion

When dealing with a small deflection such as the terminal P wave in Lead V1 there is obvious opportunity for error in measurement. Increased accuracy could of course be achieved by recording at increased paper speed and sensitivity. Because this would preclude use of the routine standard electrocardiogram for P wave analysis this was not done. The uniformity of the data, which were analyzed independently for each age group studied, and the wide divergence in measurements between normal and abnormal cases attest, however, to the validity and practicality of using standard electrocardiographic record

ing technique Others have also observed that measurements of the P V made from routine recordings are reliable.

Inadvertent cephalad placement of the Lead V electrode will result in increased negativity of the P wave unrelated to left atrial abnormality (Fig 6) Displacement of the heart such as occurs in severe over aeration of the lung will have the same effect, as will pectus excavatum Obstruction of the upper airways may also vary the *size of the negative component of the P* wave in Lead V nd in this instance an average mea urement must be made These are ll potential artifacts, unrelated to change in atrial size or hemodynamics but they must be considered in evaluating the P V relative t left atrial abnormality

On analysis of ur data very *little dif*ference is found in either amplitude or

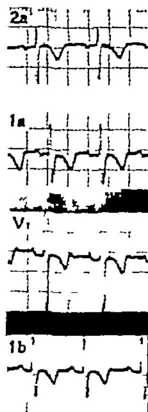


Fig 6 Normal 3-y ar old hild 1 Lead V The other three tracings re ll rec rded from an lec trode t the right ternal ed e or or t o intercost l spaces ... the Lead V electrode. 2a. T intercostal spaces abov 1 One intercostal space abov 1b One intercostal pace below

duration of the terminal component of the P wave in Lead V_1 throughout childhood (see Table II) In the different age groups, the 90th percentile for the terminal P V_1 index varies from 0 008 to 0 015 mm sec.—a very narrow range The average 90th percentile for the combined group is 0 015 and this has been arbitrarily selected as the upper limit of normal during childhood—the 95th percentile equals 0 02 There is no similarly analyzed data on adults with *which these data on children can be di*rectly compared but Morris and co-workers[4] report a 95th percentile of 0 03 for the P V_1 terminal force Their terminal measurements, however included positive as well as negative portions of the P V_1 and if only the negative component had been measured as in the present study the adult 95th percentile value might well have been even greater It appears from other studies also that terminal negativity of *P V* is normally more pronounced in adults than in children Arevalo and associates defined the adult upper limit of normal for the P V negative deflection as 1 mm. amplitude and 0 06-sec duration whereas comparable values given by Dines and Parkin are 1.5-mm and 0 04-sec. respectively

Although in borderline situations it is necessary to measure the terminal P deflection abnormal negativity of the P V_1 can often be diagnosed by simple inspection of the tracing In children if the negative portion of the P wave in Lead V exceeds one-half of a small square on ECG paper it is most probably abnormal The comparable adult value is one small square

Striking differences in P wave morphology and measurement in the right precordial leads were apparent when the normal subjects of Group I were compared with the patients of Group II having left atrial volume overload The greater incidence of diphasic P waves in Lead V and V the increased frequency with which the negative component is more prominent than the positive and the greater amplitude and duration of the terminal negative P V_1 all indicate a more posterior rotation *of the terminal P vector associated with* increased left atrial work load.

Analysis of the data on terminal P wave measurements in the group of patients indi

cates that the terminal P V₁ index is more sensitive in detecting left atrial enlargement than is either P V₁ voltage or duration alone. This is especially evident when the index is compared with the voltage measurement. For this reason use of the product of voltage and duration in assessment of left atrial abnormality is preferred.

One must consider how specifically a prominent negative P V₁ indicates left atriomegaly. In a report by Chou and Helm[8] 18 per cent of patients with pulmonary or right-sided heart disease had abnormally negative P waves in Lead V₁. Many of these instances may, perhaps, be explained on the basis of a downward displacement of the heart associated with emphysema rather than atrial abnormality. In this same report 42 per cent of patients with left atrial enlargement had an abnormally negative P V₁. There are two other references to a possible lack of specificity of negative P V₁ in indicating left atrial abnormality, but data are sparse.[3, 18] In our experience only rarely is a prominent negative P deflection in Lead V₁ unassociated with left atrial enlargement but this point requires further investigation and artifacts as indicated previously must be considered.

Comparative P V₁ measurement in patients with mild and in those with prominent left atrial overload indicates that the terminal P V₁ index is likely to be abnormal only when the hemodynamic derangement reaches a certain critical degree of severity—in only 10 per cent of the patients with mild left atrial overload was the terminal P V₁ index abnormal. It is apparent that mild degrees of left atrial overload will not displace the terminal P vector posteriorly and that abnormal negativity of the P V₁ is not an extremely sensitive indicator of left atrial abnormality. Abnormal P wave morphology is certainly even more insensitive, judged on the basis of our data. On the other hand prolongation of the P wave, which occurs in approximately one half of the patients with mild overload, is the most useful diagnostic indicator in this particular group. P:P-R segment ratio falsely positive (> 1.6) in 42 per cent of the normal tracings studied is found to be too nonspecific.

When left atrial overload is severe enough to result in combined cardiomegaly, left atriomegaly, and left ventricular hypertrophy, then the terminal P V₁ index is abnormal in virtually all (9 per cent) instances. In contrast, P wave morphology is abnormal in less than half of such patients and P wave prolongation occurs in only 5 per cent. This failure of conventional electrocardiographic criteria to correlate with the degree of left atrial load and to identify gross left atrial enlargement has been noted by others. This has limited the usefulness of the electrocardiogram in diagnosing abnormality of the left atrium.

Our data and those of Sutnick and Soloff indicate that of the various electrocardiographic measures employed in diagnosing left atrial enlargement, increased negativity of the P wave in V₁ is in fact the only one which correlates well with increased left atrial size itself.

The correlation between x-ray evidence of left atrial enlargement and electrocardiographic evidence of left atrial abnormality as indicated by the terminal P V₁ index is quite good. Eighty-five per cent of patients with a roentgenographically enlarged left atrium had a terminal P V₁ index > 0.015 and 81 per cent of those with an abnormal terminal P V₁ index had left atrial enlargement by x-ray evidence ($p < .01$). Arevalo and co-workers have also recently noted this excellent correlation in patients with rheumatic heart disease. Our study indicates that it is possible to recognize left atrial enlargement just as successfully and consistently by use of the P V₁ terminal index as by the barium esophagram and without the attendant inconvenience and radiation of the x-ray procedure.

What factor(s)—atrial enlargement, wall hypertrophy, increased intraluminal pressure, or change in anatomic position—is responsible for rotation of the terminal P vector posteriorly in the horizontal plane is uncertain. However, the evidence points to actual enlargement of the chamber. Hypertrophy of left atrial muscle seems to be unlikely as a requisite cause at least since abnormal negativity of P V₁ has been shown to occur acutely with cardiac failure[7] and we have seen it quite early in the course of a first attack of acute rheumatic carditis. In another study, left atrial pres-

sure was found not to correlate well with abnormal P V negativity A change in the anatomic position of the left atrium may be a factor but this and enlargement of the chamber may be inseparable Certainly in this study the correlation between increased roentgenographic size of the left atrium and abnormality of the terminal P V_1 index is a good one

Summary

The P wave of the scalar electrocardiogram has been evaluated in a group of normal infants and children and in a group of children with left atrial volume overload due either to ventricular septal defect or mitral regurgitation

In the normal group the P wave in Lead V was frequently diphasic with the terminal negative deflection smaller than the initial positive component however With left atrial overload the negative P V deflection becomes more prominent, and the P wave in Lead V may also become diphasic

Amplitude and duration of the terminal negative P V have been measured and their product the terminal P V_1 index obtained In the absence of left atrial overload the terminal P V index is ordinarily not greater than 0 015 mm sec the 90th percentile or one half of a small square on ECG paper Patients with left atrial overload have a significantly greater terminal P V index and can thus be identified

Abnormal negativity of the P V_1 deflection as expressed in the terminal P V index does not occur with mild left atrial overload but is consistently present with more significant degrees of overload. In a group of patients with prominent left atrial overload the terminal P V_1 index was abnormal in 92 per cent.

The terminal P V_1 index is compared with other electrocardiographic measures of left atrial abnormality Prolonged P duration is more sensitive an indicator than terminal P V_1 index but is frequently not present in patients with prominent overload Abnormal P morphology is confined to patients with more severe left atrial overload but identifies less than half the number of these who are identified by an abnormal terminal P V_1 index An increased P P R segment ratio is often a nonspecific finding

Unusual negativity of the P wave in Lead V_1 as indicated by an abnormal terminal P V_1 index correlates quite well with roentgenographic evidence of increased left atrial size. To date abnormal negativity of the P wave in Lead V_1 is the sole electrocardiographic measure of left atrial enlargement which has this advantage.

The help of Dr B C Faul in recording the electrocardiograms of premature infants is gratefully acknowledged

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Response of pulmonary blood volume to 64 to 114 weeks of intermittent stay at high altitudes

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Fishman in a recent editorial has rightly remarked that progress in the understanding of the role of pulmonary blood volume in the regulation of the circulation was hampered by nonavailability of a reliable technique for accurately measuring the pulmonary blood volume. The precise estimation of the pulmonary blood volume in man became feasible when transseptal left atrial catheterization was accepted as a safe procedure and injection of the indicator dye into the left atrium could be utilized for the recording of arterial dye-dilution curves.[4] Since then the response of the pulmonary blood volume to exercise, acute hypoxia, inhalation of 100 per cent oxygen, change in body position, and various pharmacologic agents has been extensively studied, but data on the response to high altitude chronic hypoxia are not available. The purpose of the present communication is to present observations on the response of the pulmonary blood volume in man to a long-term intermittent stay at high altitude.

Material and method

Pulmonary blood volume and related hemodynamic parameters were estimated in 11 healthy male volunteers by combined right and left heart catheterization at sea level (650 feet) before and after 64 to 114 weeks of intermittent stay at an altitude of 14,500 feet. The subjects were 19 to 27 years old at the beginning of the study, with an average age of 21 years. They were studied in the fasting state without sedation. Right heart catheterization was performed by positioning a No. 7 cardiac catheter in the pulmonary artery just beyond the valve. The left atrium was entered by the percutaneous Brockenburgh transseptal method as practiced in this laboratory.[11] The right brachial artery was cannulated in order to obtain arterial blood pressure and dye curves. The pulmonary blood volume (PBV) was estimated by methods described by Dock and associates and Milnor and associates.[4] Consecutive dye-dilution curves were obtained directly on a Poly Viso channel

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through a continuous recording densitometer (Colson) by injecting 5 mg of indocyanine green dye first into the left atrium and then into the main pulmonary artery in 6 subjects, and in reverse order in the other 5 subjects. The difference between the mean transit times of the two resulting curves was taken as the pulmonary transit time. The cardiac output was measured from the dye-dilution curves by replotting the dye concentration against time on a semilogarithmic basis and utilizing the Hamilton Stewart method.[11] The volume of blood between the pulmonary artery and the left atrium was obtained by multiplying the pulmonary mean transit time by the average cardiac output, and this represented the PBV. Similarly the volume of blood between the pulmonary artery and the brachial artery was obtained by multiplying the pulmonary artery to brachial artery mean transit time by the average cardiac output and this represented the central blood volume (CBV).

Table I. Data on duration of total and continuous stay at high altitude and time interval between the two studies

Subject	Date of study	Age (yr.)	B.S.A. (M.²)	Total stay (weeks): Altitude	Total stay (weeks): Plains	Number of ascents	Last continuous stay at high altitude (weeks)	Interval between departure from high altitude and study (hours)
1	Sept 13 1963	19	1.66	80	25	4	10	47
	Oct 13 1965	21	1.69					
2	Sept 3 1963	19	1.76	90	14	3	21	46
	Sept 14 1965	21	1.76					
3	Sept 2 1963	21	1.76	97.5	19	4	22	48
	Dec 16 1965	23	1.74					
4	Sept 9 1963	20	1.82	98.5	18.0	4	23	48
	Dec 18, 1965	22	1.84					
5	Sept 7 1963	21	1.68	97.5	18.5	4	31	46
	Dec 17 1965	23	1.66					
6	Sept 17 1963	27	1.66	114	15.0	5	31	48
	Mar 13 1966	29	1.68					
7	Sept 9 1963	25	1.66	103	14.0	3	41	46
	Dec 12 1965	25	1.68					
8	Sept 18 1963	20	1.70	110	15	3	42	48
	Feb 26 1966	2[illegible]	1.80					
9	Sept 5 1963	19	1.60	111	19	3	42	90
	March 3 1966	21	1.68					
10	Sept 6 1963	2[illegible]	1.64	64	61	4	43	120
	Feb 26 1966	24	1.68					
11	Sept 16 1963	20	1.72	98	10	2	49	7[illegible]
	Oct 10 1965	2[illegible]	1.70					
Average		21	1.70	97	20.3	3.6	33.5	80
		23	1.73					

Details of the technique are reported elsewhere. The intracardiac and brachial arterial pressures were recorded through Statham P23AA strain gauge manometers on a 4-channel single-gun photographic system. The base line for all measurements of pressure was taken as half the thickness of the chest at the second costal cartilage with the patient supine.[13]

After 64 to 114 weeks of total intermittent stay at an altitude of 14 500 feet the 11 subjects were restudied within 46 to 120 hours of their final departure from high altitude. The interval between the two studies was 105 to 129 weeks. All subjects had 1 to 4 interruptions of the stay at high altitude when they proceeded on leave to the plains. Every subject therefore went up to high altitudes 2 to 5 times. Their total duration of stay on the plains lasted between 10 and 62 weeks. The details of their total duration of stay at high altitude and on the plains, and related data are outlined in Table I. None of the subjects had suffered from high altitude pulmonary edema or hypertension.

Table II. Hemodynamic Data

Subject	Heart rate		Cardiac index		Stroke index		Central blood volume	
	Per min	Change	L/min/M	% Change	ml/beat/M	% Change	ml/M	% Change
1	54	0	1.9	+16	35	+17	696	+19
	54		2.2		41		827	
2	72	−25	3.3	+21	46	+61	733	+72
	54		4.0		74		1 260	
3	60	+10	2.5	+128	42	+104	612	+179
	66		5.7		86		1 710	
4	75	−4	3.2	+38	43	+42	746	+60
	72		4.4		61		1 195	
5	72	−17	3.4	+50	47	+81	938	+50
	60		5.1		85		1 411	
6.	72	+25	3.2	−90	44	+23	778	+58
	54		2.9		54		1 218	
7	66	+18	3.1	+61	47	+36	555	+134
	78		5.0		64		1 295	
8.	75	−4	3.0	+87	40	+95	615	+143
	72		5.6		78		1 497	
9	90	−17	3.6	+75	40	+117	887	+103
	75		6.3		87		1 795	
10.	72	−10	2.1	+186	29	+214	630	+186
	66		6.0		91		1 801	
11	72	−32	2.7	+4	38	+53	610	+57
	48		2.8		58		961	
Average	71	−10	2.9	+60	41	+77	709	+97
	62		4.5		71		1 361	

and their physical electrocardiographic and roentgenologic examinations prior to the restudy were normal.

Results

1 Heart rate pulmonary flow pulmonary and central blood volumes The heart rate decreased significantly (17 to 32 per cent) in 5 subjects and increased by 17 per cent in 1 subject (Table II) The pulmonary flow exceeded the upper limit of our normal values (5 0 liters per minute per square meter of body surface area) in 4 subjects (5 6 to 6.3 liters per minute per square meter) but some increase (16 to 186 per cent) in the flow was seen in 10 subjects, the average increase being 60 per cent (Fig 1) Because of some decrease in the heart rate and increase in the flow values for stroke output showed a consistent increase (17 to ?14 per cent average 77 per cent) The average increment in the CBV values was 97 per cent (19 to 186 per cent) and that in PBV was 76 per cent (3 to 193 per cent)

2 Duration of stay blood volumes and

Pulmonary blood volume		Mean pulmonary arterial pressure		Mean left atrial pressure		Pulmonary vascular resistance	
ml/M	% Change	mm Hg	% Change	mm Hg	% Change	mm Hg/L/min/M	% Change
310		12		7 0		2 6	
	+ 3		0		− 29		+19
319		12		5 0		3 1	
330		15		6 0		2 7	
	− 45		+20		0		+11
217		18		6 0		3 0	
236		14		6 0		3 2	
	+ 33		−14		0		−66
314		12		6 0		1 1	
218		14		7 0		2 1	
	+ 61		+21		+ 6		0
352		17		8 0		2 1	
352		11		6 0		1 4	
	+ 77		+45		+ 33		+ 7
621		16		8 0		1 5	
272		11		4 0		2 2	
	+ 60		+36		+125		−23
435		15		10 0		1 7	
131		15		5 0		3 2	
	+ 65		+20		+100		−50
215		18		10 0		1 6	
175		15		4 0		3 7	
	+169		0		+ 50		−57
471		15		6 0		1 6	
310		12		5 0		1 9	
	+ 66		+42		+ 20		−11
514		17		6 0		1 7	
263		15		8 0		3 3	
	+193		+ 8		− 13		−54
764		16		7 0		1 5	
179		16		7 0		3 3	
	+157		+13		+ 36		−12
442		18		10 0		2 9	
259		11 6		6 0		7 7	
	+ 76		+17		+ 21		−21
437		16 0		0		2 0	

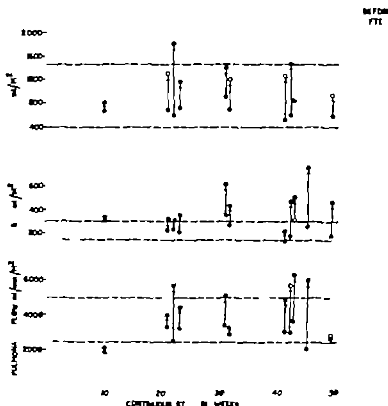


Fig. 1. Pulmonary blood volume, central blood volume, and pulmonary flow estimated in 11 volunteers before and after their stay at high altitude are plotted against their last continuous stay. The areas between the dashed lines are the ranges of our normal values. Normal values in this and subsequent figures relate to the values obtained by studying 25 healthy male volunteers of comparable age and occupation.

pulmonary flow. The progressive increment in the values of the PBV could be related to the duration of the last continuous stay (Fig. 2). Thus, the average increase in PBV of the 4 subjects with a stay of less than 25 weeks was 11 per cent, whereas that of the 3 subjects with a stay of 35 to 44 weeks was 95 per cent. Values for central blood volume, on the other hand, increased by 123 per cent within the first 5 weeks of stay and remained high, with some fluctuation, throughout the stay. Pulmonary blood flow followed a pattern similar to that of CBV, but the increase was not of equal magnitude. Although the increase in the central and pulmonary blood volumes (but not pulmonary flow) could also be related to the total duration of intermittent stay (Fig. 3), a better relationship could be established with the duration of the last continuous stay. Thus, Subject No. 10, who had the shortest total stay of 64 weeks but a long continuous stay of 45 weeks, had considerable elevation of all the values, in contrast to Subject No. 6, who had the longest total stay of 114 weeks but only 31 weeks of continuous stay and proportionately less increase in the values. Also, the number of interruptions did not affect the response of the pulmonary vascular dynamics, as demonstrated by Subjects No. 10 and 11, who had 4 and 1 interruptions, respectively.

3. Duration of stay and pressure values. The pulmonary arterial mean pressure decreased in 1 subject, did not show any alteration in 2, and increased 8 to 45 per cent in the other 8 subjects. The average increase was 17 per cent; the increase in no instance was more than 5 mm. Hg, and the values were within the upper limit of our normal values of 19 mm. Hg. Similarly, the left atrial mean pressure decreased in 2 subjects, did not change in 2, and increased 6 to 125 per cent in the other 7 subjects. The average increase was 25 per

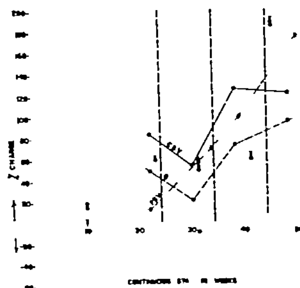


Fig. 2 Changes in pulmonary flow and pulmonary and central blood volumes (expressed as percentage) of the 11 volunteers related to their continuous stay at high altitude. The percentage change in the values of PBV, CBV and pulmonary flow are indicated, respectively, by the crosses, solid circles, and open circles. The average values of the four periods of stay (under 25 weeks, 25 to 34 weeks, 35 to 44 weeks, and over 44 weeks) are denoted by asterisks for PBV, by solid circles with slit for CBV, and by open circles with bar for pulmonary flow. An increase in the CBV and pulmonary flow is seen within 25 weeks of stay, whereas the increase in PBV is apparent only after that period, whence it progressively increases.

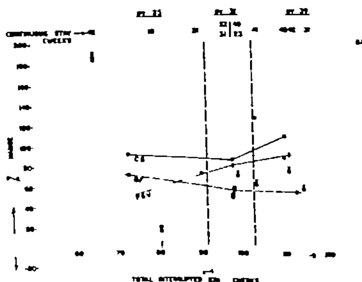


Fig. 3 Percentage changes in the values of pulmonary flow (*open circles*), PBV (*crosses*) and CBV (*solid circles*) related to the total duration of interrupted stay grouped into three periods of stay, i.e., up to 90 weeks, 91 to 102 weeks, and more than 102 weeks. Average values of PBV, CBV, and pulmonary flow during each period are indicated by asterisk, solid circles with slit, and open circle with bar, respectively. Although some increase is seen in the CBV and PBV (but not flow) values when related to the total stay, better correlation is apparent with the continuous stay shown at the top of the figure.

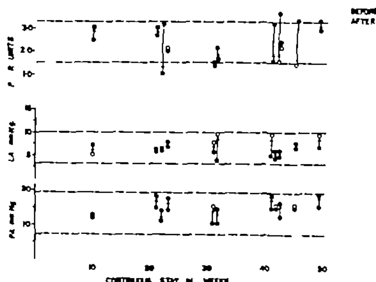


Fig. 4. Values for pulmonary arterial and left atrial mean pressures and pulmonary vascular resistance estimated in 11 volunteers before and after their stay at high altitude are plotted against their last continuous stay. Although some increase in pulmonary arterial and left atrial mean pressure values are seen in the majority of the volunteers, in no instance has the value exceeded the upper limit of our normal values (19 mm. Hg for pulmonary arterial mean and 10 mm. Hg for left atrial mean) as shown by the top dashed lines. Values for pulmonary vascular resistance are lower because of increased pulmonary flow.

cent, but all of the values were within the normal range of 10 mm. Hg as shown in Fig. 4. Because of increased flow, pulmonary vascular resistance decreased in 7 of the 11 subjects. The slight increase in the pulmonary arterial and left atrial mean pressure values could not be related to the duration of the total or the intermittent stay.

Discussion

When healthy males were exposed to an altitude of 14,500 feet intermittently for 64 to 114 weeks, their pulmonary blood volumes increased significantly. However, the reliability of assessments of the changes in the PBV depends upon the validity of the technique utilized to estimate the volume. Samet and co-workers recently compared the true pulmonary blood volume in 96 subjects by three different dye-dilution methods: (1) difference between the pulmonary-artery–systemic artery volume and the left atrium–systemic artery volume (as utilized here), (2) pulmonary-artery to left atrium volume as determined by injecting into the pulmonary artery and sampling from the left atrium, and (3) difference between the right atrium–left atrium volume and the right atrium–pulmonary-artery volume. The authors found that the first and the third methods yielded comparable results, whereas the second method gave much higher values and postulated that a mixing ventricle was necessary for the dye-dilution technique to yield reliable values of pulmonary blood volume. Since Samet and associates' Method 1 has been utilized in the present study and since every subject acted as his own control, the changes in the values for pulmonary blood volumes observed here appear to be reliable. The other changes seen in the pulmonary vascular dynamics are a significant increase in the pulmonary blood flow and central blood volume, but the pressure values show only a slight increase. The present findings are somewhat different from those of Rotta and associates.[7] They observed an increase not only in the cardiac output and total blood volume (thereby postulating an increase in PBV), but also in the pulmonary arterial pressure in temporary residents of high altitude. Because control data on their subjects at sea level were not available, the significance of the actual changes in the various parameters cannot be esti-

mated Although some data on the response of the PBV to acute hypoxia are known estimates of the PBV before and after long term intermittent exposure to high-altitude hypoxia are not available hence data on the response of the PBV as presented in this study cannot be critically reviewed

When the increments in the values were related to the total and continuous stays at high altitude a more satisfactory correlation existed with the continuous stay than with the total stay Since the subjects had 1 to 4 interruptions of their stay at high altitude the response of their pulmonary vascular dynamics could have been more appropriately related to the total or the continuous stay if the values had been repeatedly estimated at the end of each period of continuous stay Although this would have been ideal it was not possible. Some relationship was apparent between the increments in the values of pulmonary and central blood volumes and the duration of total stay when grouped into three different periods up to 90 weeks, 91 and 102 weeks and more than 102 weeks. On the other hand when the increments in the values were similarly related to periods of 10 weeks of continuous stay a more significant trend emerged Both CBV and pulmonary flow values increased significantly within the first 25 weeks of stay and remained increased with some fluctuation throughout the stay but the increment in PBV was apparent only after 25 weeks of stay after which period it progressively increased However it is to be noted that the number of observations in each period of 10 weeks of continuous stay was too small for the drawing of any firm conclusion In a previous study differences in the responses of CBV and PBV were also observed in convalescents from high-altitude pulmonary edema and high-altitude pulmonary hypertension. The CBV in both of the groups was grossly elevated but the PBV of the hypertensive group was normal and that of the edema group was significantly high Monge and co-workers also found that the PBV when compared to the CBV was disproportionately higher in the natives of the Peruvian Andes than in residents of sea level. Such different response of PBV and CBV would indicate that an increase in the PBV is independent of an increase in CBV and may represent a form of homeostasis between the pulmonary and the extrapulmonary blood volumes.

Although considerable changes were recorded in the blood volumes and pulmonary flows as a response to high altitude the pressure values did not show significant elevation Pressure values obtained in this study should be interpreted cautiously since the pressures were not recorded at the altitude of 14,500 feet but at sea level (650 feet). Although Peñaloza and his associates have demonstrated a reduction in the pulmonary arterial pressure values of natives of the Peruvian Andes who were restudied after having been stationed at sea level for over 2 years data on the immediate changes in the pulmonary arterial pressure values in subjects descending from high altitude to sea level are sparse. Rotta[11] reported the circulatory changes seen in a native of the Peruvian Andes who was studied at an altitude of 14 900 feet and again after 8 days of residence at sea level He found that the mean pulmonary arterial pressure decreased from 26 to 15 mm Hg (neither the pulmonary arterial wedge nor the left atrial pressure was recorded) Therefore from the present data it is not possible to predict what the pressure values might have been had they been measured at high altitude. However 8 of the 11 subjects were restudied within 48 hours of their departure from high altitude and if there had been any significant elevation of the pulmonary arterial pressure it would have been possible to document it in some of them Furthermore, routine 14-lead electrocardiograms recorded every month in these 11 subjects did not reveal any evidence of right ventricular hypertrophy Hence although it is not possible to state categorically that the present subjects did not have some significant elevation of pulmonary arterial pressure at while they were at high altitude the circumstantial evidence appears to be against it. Thus, it would appear that when these healthy persons were stationed at an altitude of 14,500 feet in the Himalayan terrain intermittently for 64 to 114 weeks, they had elevated pulmonary flow and pulmonary blood volume but normal pressure values

which might represent a form of successful adaptation to high altitude hypoxia

Summary

Data on the pulmonary blood volume and related hemodynamic parameters obtained by cardiac catheter studies in 11 healthy volunteers before and after 64 to 114 weeks of intermittent stay at an altitude of 14 500 feet have been presented

The heart rate decreased by 13 per cent pulmonary flow increased by 60 per cent and stroke volume increased by 77 per cent The central and pulmonary blood volumes showed an average increase of 97 and 76 per cent respectively Pulmonary arterial and left atrial mean pressure values showed some elevation but remained within the upper limits of our normal values.

When the increases in the flow and blood volumes were related to the duration of total and continuous stays at high altitude better correlation was apparent with the last continuous stay prior to the restudy than with the total stay Although central blood volume and pulmonary flow increased within 25 weeks and remained increased with some fluctuation the increase in the pulmonary blood volume was apparent only after 25 weeks of stay after which it increased progressively

It is suggested that increased pulmonary flow and pulmonary blood volume but normal pulmonary arterial pressure as seen here may represent a form of successful adaptation in temporary residents of high altitude

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The pathologic basis of the electrocardiographic pattern of parietal block

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The term "parietal block" has occupied a prominent place in the electrocardiographic literature during the last decade. The electrocardiographic patterns which are considered characteristic of parietal block have been found in ischemic myocardial disease,[1] infectious myocardiopathies, congenital disease,[3] metabolic and toxic diseases,[4-] and cardiac myopathies of unknown origins.[12] Their onset has been observed acutely after surgical trauma,[13] myocardial infarction, and angina pectoris.[14] There have been reports of the rare appearance of this pattern in apparently healthy young men.

Grant and associates suggested that parietal block might be caused by an interruption of the anterior radiation of the left bundle branch with left ventricular depolarization that occurs principally through the posterior radiation of the left bundle branch and the anterior radiations distal to the interruption being activated via interdigitations between the 2 systems. Sampson and Bruce[1] observed the acute onset of parietal block in patients who undergo aortic commissurotomy and suggested that this might be caused by the damage to the anterior radiations of the left bundle branch as they coursed superficially in the septum in the area of the aortic outflow tract. Past studies in this laboratory[19] of 50 hearts with "parietal blocks" have suggested that the conduction abnormalities in most of the above mentioned disorders were caused by scattered fibrosis and disruption of the distal Purkinje network and hence were fittingly called parietal. However, no detailed examinations of the specialized conduction systems were made in these specimens.

We have had occasion to examine 15 hearts of patients with various acute and chronic diseases who had electrocardiograms that showed left axis deviation and parietal block. Because the specific region of the anatomic lesion that is associated with the conduction defect is still very much in doubt, it was elected to study these hearts by serially sectioning their specialized conduction system and examining multiple step sections through the ventricu-

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lar walls of these same hearts. This report describes the results of this study

Methods

The hearts of 15 patients, who had had electrocardiograms showing left axis deviation during life and who were autopsied between July 1963 and January 1965 were examined in detail After gross examination the upper part of the ventricular septum was removed as a block in each of these hearts and serially sectioned placed on 35 or 70 mm plastic tape in the manner described by Fickett and associates,[n] and stained with Masson s trichrome stain The remainder of the heart was sectioned by regions three sections of the anterior wall (basal mid apex) three sections of the lateral wall three sections of the posterior wall two sections of the right ventricle and the apex of the heart. In addition sections of the mid and inferior interventricular septum were taken.

The serial electrocardiograms of all the examined patients were evaluated as to the degree of conduction delay and other electrocardiographic abnormalities. An electrocardiogram was accepted as fitting the criteria for parietal block and left axis deviation when the mean axis in the frontal plane was −15 degrees or more and when there was a broad angle between the initial and terminal vectors (Fig 1) Electrocardiograms of the $S_1S_2S_3$ variety were eliminated from this study

Results

The results of the histologic examination are summarized in Table I The distribution and range of severity of lesions varied widely No particular region of the myocardium was involved with greater frequency than any other region and there were 3 cases with no histologically detectable lesion Table II demonstrates the random distribution of significant (+ or more) lesion in a our areas of the left ventricular wall ventricular septum and conduction system Hypertrophy was present in 9 of the 15 hearts but was never the only demonstrable lesion its role in the genesis of the defect therefore is difficult to delineat

The cause of the cardiac disease (Table III) was heavily weighted toward myocardial infarction Significant arteriosclerosis without infarction was not found in any of our cases.

Discussion

Two basic explanations for this electrocardiographic pattern have been postulated in the past (1) interruption of the anterior projections of the left bundle branch and (2) lateral wall damage leading to delayed activation of the free wall and subsequent vectorial shift to the left and posteriorly Association of these patterns with diffuse disease of the entire myocardium has caused others to doubt the specificity of the electrocardiogram in implicating a single anatomic region[n] or cause (i e myocardial infarction) In addition Lenegre[n] failed to find any specific focus of the left bundle consistently involved in the conduction abnormality which he described as incomplete left bundle branch block.

In this series, we have examined left axis deviation of recent onset and that which has existed throughout the length of time the patient was followed at our hospital. Our experience has been that a variety of conditions are associated with left axis deviation. To determine whether or not left axis deviation resulted from these conditions affecting a common anatomic site, we embarked upon a detailed histologic study of hearts from patients who demonstrate the ECG pattern In each case, systematic sections were taken through the ventricular myocardium In addition the main portion of the specialized conduction

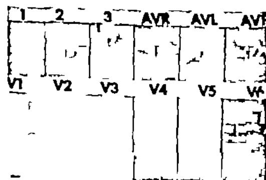


Fig 1 Electrocardiogram of Patient 3 man with severe coronary artery disease which demonstrates the general pattern of parietal block.

Table I. Summary of main pathologic findings

Case No.	Conducting system: AVN*	Conducting system: CB	Conducting system: LB	Conducting system: RB	Left ventricle: Ant. 1	Left ventricle: Ant. 2	Left ventricle: Ant. 3	Left ventricle: Lat. 1	Left ventricle: Lat. 2	Left ventricle: Lat. 3	Left ventricle: Post. 1	Left ventricle: Post. 2	Left ventricle: Post. 3
1	0	0	0	0	0	0	+ F	+ F	+ F	+ F	+++ F	0	0
2	0	0	0	0	0	+++ fib.	+++ fib.	0	+++ fib.	+++ fib.	0	+++ fib.	0
3	0	+ hem	+ hem	0	0	± SE nec	± SE nec.	0	0	± SE nec	0	± SE nec.	0
4	—	—	—	—	0	0	0	0	0	0	0	0	0
5	+F CI	+F CI	+F CI	+F CI	+	+	+	+	+	+	+	+	+
6	0	+ hem	0	+ hem.	0	0	++++ fib.	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	± fib.	0	0	± fib.	0	0	± fib.	± fib.	0	+ fib.	+ fib.	
9	0	± fib	++ fib.	+++ fib.	++ fib	+ fib.	± fib.	+ fib.	+ fib.	0	0	0	0
10	0	± fib.	+++ nec.	0	+++ fib.	+ nec.	0	+ fib.	+ fib.	+ fib.	+++ fib.	+++ fib.	+++ fib.
11	0	+ hem	0	0	+ fib.	+ fib.	++ org	+ org	+ org	0	+ fib.	++ org	++ org
12	0	0	0	0	0	+ fib	+ fib.	0	0	0	+++ fib.	+++ fib.	0
13	0	0	0	0	0	++ fib.	++ fib.	—	—	—	0	+++ fib.	+++ fib.
14	+ CI	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	Ac. MI distal	0	++++ fib	0	± fib.	++ fib.	++ fib.	0	+ fib.	++++ fib.	++++ fib.

Abbreviations: ac, acute; AVN, atrioventricular node; CB, common bundle; epi., epicardium; F, focal; fib., fibrosis; hem., hemorrhage; org., organizing; RB, right bundle; RHD, rheumatic heart disease; RV, right ventricle; SE, subendocardial.
†Scattered foci of acute and chronic inflammation and necrosis. 1, base; 2, mid; 3, apical.
Grading of lesions: 0, normal; ±, very slight; +, slight; ++, moderate; +++, marked; ++++, very marked.

system was serially sectioned in order to find lesions of limited size that otherwise could be overlooked with random step sectioning. There is no evidence that damage to any specific portion of the conduction system is involved in all cases of left axis deviation, although the findings in case 10 (Fig. 2), in which there was an acute onset of the left axis deviation after surgery adjacent to the left ventricular septum, suggest that damage to the left bundle may indeed be related in some cases as suggested by Sampson and Bruce.[13] In addition, the finding of left axis deviation in one patient with intermittent second and third degree A-V block suggests that conduction of the abnormalities system may play a prominent part in some cases of left axis deviation.

A significant number of hearts from patients who had left axis deviation contain no anatomic abnormalities of the con-

IVS 2	3	RV	Other	Ht., wt g	M in diagnosis
+++ F	0	0	+++epi.	575	RHD old MI post. LV and IVS
++ fib	0	0	—	450	Old MI ant. and lat. LV
± SE	0	0	—	380	Ac. MI by EKG, not confirmed post mortem
nec. 0	0	0	—	400	Diabetic acidosis
+	+	+	+++epi	720	Aortic stenosis and subac. bact. endocarditis
++ nec	+++ fib.	0	Perf of IVS	400	Old nd recent MI ant. pical LV and IVS
+ fib.	0	0	—	340	Normal heart Hodgkin disease
+ fib.	0	0	—	325	Ca of colon
+ fib.	++ fib.	0	Small ac MI IVS	390	Marked coronary arteriosclerosis
++ fib.	+++ fib	0	—	810	Old MI post. LV nd IVS
+++ nec	+++ nec	0	—	550	Ac MI ant. pical IVS old and org MI LV
++++ fib.	++++ fib.	0	—	271	Mkd cor sclerosis old MI pex LV and IVS
+++ fib	++++ fib.	0	Small ac MI t. LV	600	Old MI pex LV and IVS
+++ fib.	0	0	—	518	Old MI base IVS Ca pancreas
Ac MI base		0	—	—	Old MI ant. and post. LV ac. MI base IVS

ht heart IVS interventricular septum LAT lateral LB left bundle LV left ventricle MI myocardial infarct nec necrosis, org

duction system on serial sectioning In these patients it is difficult to associate lesions in any one region of the myocardium with the conduction defect since there is no specific region which is more frequently involved than any other It must be postulated therefore that left axis deviation and parietal block may also result from myocardial lesions which are either diffuse or scattered The extent of the anatomic abnormalities associated with these defects may vary from extensively damaged to histologically normal hearts.

It is possible either that the histologically normal hearts with left axis deviation (Fig 3) have lesions that are too subtle to be detected by routine histologic studies or that anatomical variants resulting in unusual conduction[13] may be more common than heretofore realized. It is noted that the electrocardiogram from the 3 histologically normal hearts showed no slurring

Table II Position of cardiac lesions associated with parietal block

Position of lesion	N
I terior left entricle (+ or m re)	9
In posterior left ent icle	8
In lateral left entricle	6
I interventricular sept m	12
I A V node	1
In common bundle	4
In left bundle branch	5
In right bundle branch	2
No significa t les on (+ or less)	3
Hypertroph (> 4 5 Gm)	7

Table III An itom c diagnoses in this series

Anatomic diagnos	N
M ocardial nf t (old)	10
M ocardial f rct (ac t)	2
V h lar disease (ithout surgery)	1
V l la disease (postoperativ)	1
Infect ous d sease (SBE)	1
Complet heart block	1
N cardiac dise se	3

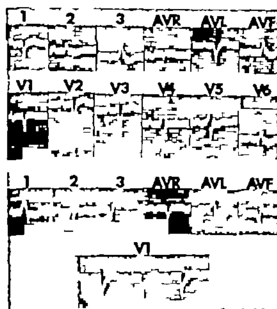


Fig Electrocardiograms taken preoperati l (A) and postoperatively (B) of P tient 10, oma ho developed left ard shift of the electrical axis fter aortic val surgery Not that terminal vector remains t right

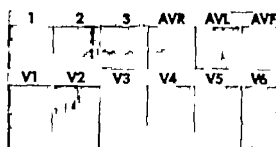


Fig 3 Electrocardiogram of Patient 7 a histologically normal heart Note the lack of slurring or prolongation of QRS

or prolongation (Fig 3) and thereby differ from those that were seen in the presence of heart disease (see Fig 1) This may prove to be a useful clue in differentiating left axis deviation in normal hearts from that in abnormal hearts.

Summary

Extensive pathologic examination of hearts of patients with parietal block and varying clinical pictures indicates that parietal block and left axis deviation can result from a variety of anatomic lesions and that no specific area of the heart or conduction system is consistently involved

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Experimental and laboratory reports

Electrocardiographic distortions caused by inadequate high frequency response of direct writing electrocardiographs

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It is well known that inadequate frequency response of a recording system may introduce errors in amplitude and wave shape into the electrocardiogram. Since A.C. recording systems are generally used, both the low frequency and high frequency characteristics can affect the integrity of the recorded output. Errors caused by the inadequacy of the low frequency response of electrocardiographs are to be found mainly in the ST-T and T wave areas of the electrocardiogram and have been reported upon by several investigators.[1-3] The high frequency characteristics of the recording system will affect mainly the QRS complex, because it is in *this part of the electrocardiogram that the* components of higher frequency are to be found.

Recommendations on high frequency response of electrocardiographs have come from various sources. Einthoven suggested a response time of 0.01 second. Rappaport and Rappaport recommended a response time of 0.0015 second. The committee on electrocardiography of the American Heart Association in 1954 recommended a frequency response of about 50 c.p.s.† for direct writers. Dower and co-workers, in a review of this subject and in a study of electrocardiograph characteristics, have recommended that direct writers should maintain a cutoff frequency of at least 100 c.p.s. Although response time is usually defined as the time required for the output to rise from 10 to 90 per cent of its final value in response to a direct-current input, *these authors have also pointed out the* difficulty of relating response time to frequency performance. Using an approximation to establish a relationship between these two performance indicators, they

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†This report states: "When the instrument is adjusted for a maximum deflection of 1 cm. in response to a direct voltage of 1 millivolt, the deflection resulting from a sinusoidal voltage of the same magnitude varying in frequency from 1 cycle to 15 c.p.s. shall not be less than 0.9 cm.; from 15 to 40 c.p.s., shall not be less than 0.8 cm."
Note: The term Hz has been recently designated the preferred term; however, the term c.p.s. has been used throughout this paper, for time did not permit change in typeset material after the revision was announced.

tabulated the recommendations for high frequency response that have been made from these various sources

Langner Geselowitz and co-workers [10] have reported that a high frequency response of the order of 500 c.p.s. is necessary in order to resolve the fine detail in the low amplitude high frequency notches and slurs that occur in the QRS complex. With direct writers however it is generally impossible to record at such frequencies with any degree of integrity The high frequency response of the majority of direct writing electrocardiographs presently used is well below 100 c p.s. The recording of electrocardiograms with instruments having a high frequency response below 100 c.p.s. may lead to significant errors in amplitude and duration in the well defined Q R, and S waves, aside from the notches and slurs of higher frequency The purpose of this study is to evaluate these distortions that may be caused by the inadequacy of the high-frequency response of direct writing instruments

Method

Electrocardiograms, taken from a series of 20 subjects consisted of 10 normal and 10 abnormal records. The Frank lead system[11] was used for record ng so that a total of 60 tracings 3 per subject, were used for study (For the purpose of this study the selection of a particular lead system is of no importance since poor performance of a recording system will cause distortion in the ECG of any lead.)

These records were initially recorded onto FM magnetic tape where the band width of the entire record and playback system including preamplifiers was 0 05 to 1 250 c.p.s. (3 db down) Each record was then passed through a low pass filter which simulated a recording system having a lower frequency response and the filtered output was compared to the original waveform The comparison was always made using the same complex for the original and filtered waveforms. The characteristics of the low-pass filter were adjusted to permit the high frequency cutoff (3 db down) and the slope or rolloff † to be varied independently Twenty-one different high-frequency characteristics were used for recording each record as shown in Fig 1

*The most accepted definition for high frequency cutoff is the frequency at which the amplitude response of a system is 0.707 of its f ll response at lower frequencies. This is the definition used here. Decibel (db) response is related to voltage response by the formula $db = 20 \log \frac{\text{Voltage output}}{\text{Voltage input}}$ Thus, an output-to-input voltage ratio of 0.707 is equivalent to 3 db

†The term "rolloff or slope refers to the rate of ttenuation of output amplitude beyond the cutoff frequency It is often expressed in units of db per octave, meaning the number of decibels difference between the response at one frequency and that at twice that frequency The simplest resistance-capacitance network gives rise to 6-db-per-octave slope, and when networks like this are used in tandem, the rate of attenuation increases accordingly Normally no resonant peaks are present that is, the response shows steady decrease in amplitude as frequency increases However some systems are purposely designed improve the response time while maintaining the same cutoff frequency This may result in resonant peak appearing in the frequency response The resonant frequency is that frequency at which the response is maximum. The 24-db-per-octave curv shown in Fig 1 demonstrates the manner in which resonance may occur

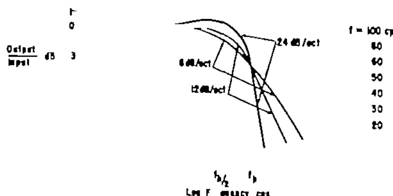


Fig 1 Frequency response characteristics of the low-pass filters used to simulate the high-frequency performance of direct writing electrocardiographs. f is the frequency t which the response is ttenuated 3 db from its low frequency response.

The low pass filters that were used to simulate various high frequency response characteristics were of three basic types. The 6-db-per-octave filter consisted of a simple RC network (see Fig. 2) built around an operational amplifier. The 12-db-per-octave filter was composed of two such networks in tandem and the 24-db-per-octave characteristic was obtained using a Krohn Hite variable filter (Model 335). The 6-db-per-octave and 12-db-per-octave characteristics were simple rolloffs with no resonant peaks but the Krohn Hite filter does have a resonant peak of about 1 db occurring approximately 1 octave below the cutoff frequency (see Fig. 1).

In order to prepare these records for handling by a digital computer, they were first converted into digital records using an analog-to-digital converter. The converter output consisted of digital magnetic tape, each record of which held the simultaneous samples of the original and filtered waveforms. A 1 millisecond sampling rate was used for each analog input with a precision in sampling of one part in 1,024. A block diagram of the conversion process is shown in Fig. 3.

A Control Data Corporation 3200 digital computer was used for the analysis of the digital magnetic tape records. The following parameters were measured for each record: (1) peak Q amplitude, (2) peak R amplitude, (3) peak S amplitude, (4) Q/R and R/S ratios, (5) QRS duration, (6) Q duration, (7) duration from the beginning of Q to the peak of R (R peak time), (8) Q-T interval, (9) P-R interval.

A calibration signal was recorded preceding each ECG and each amplitude measurement is referred to its proper calibration signal.

In the evaluation of the error for each of these parameters, measurements made

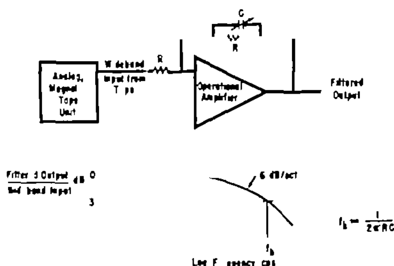


Fig. Circuitry used for the simulation of 6-db-per-octave low-pass filter. The value of the capacitor may be varied to obtain the desired cutoff frequency. The 12-db-per-octave simulation consisted of two such circuits in tandem with the RC of each circuit adjusted so as to provide 1.5 -db attenuation each at the frequency f.

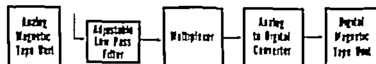


Fig. 3. Block diagram of the method of conversion from analog-to-digital data. The multiplexer permits essentially simultaneous sampling of the wide-band and filtered records so that identical complexes can be studied.

on the wide-band unfiltered records were taken to be the true values. Measurements made on the identical complex of the filtered record were compared with these true values, and any deviations are regarded as errors caused by the limited frequency response of the recording system

Results

The measurements made in this manner revealed the following general characteristics

1 QRS time durations were affected relatively little by high frequency performance of the recording system but could be considered to be significant when the frequency response was reduced below 60 c p.s. Other time interval measurements were affected in much the same manner as QRS durations

2 Amplitude errors in Q R and S waves were directly related to the high frequency response characteristics. In general the errors increased as the cutoff frequency decreased and a steeper rolloff caused more errors than did a more gradual one for the same cutoff frequency

3 Amplitude values were more often decreased as the high frequency cutoff was reduced however there were a number of records in which increased amplitude values were observed particularly with th 24-db-per-octave filter

4 Parameters such as Q R or R S ratios were affected in a similar manner by cutoff frequency and rolloff

5 Both normal and abnormal records were similarly affected by the high frequency response characteristics of the recording system

Table I lists the percentage of records which exhibited QRS duration errors. Decreasing the cutoff frequency generally results in more errors A certain variability exists in the interpretation of the beginning and the end of a QRS complex. In this case the interpretation was performed manually using enlarged digital plots of the electrocardiograms, and only those errors greater than 10 milliseconds were recorded Reference to Table I leaves little doubt however that significant errors can result when high frequency cutoffs below 60 c.p.s. are used These errors result mostly in increased QRS durations with a small number of records showing decreased durations at cutoff frequencies of 20 and 30 c.p.s. It appeared that the 12-db-per-octave characteristic was more desirable than the 6-db-per-octave response although either system produced significant errors when the cutoff frequency was reduced below 40 c p.s. This could be explained by noting that, for the same cutoff frequency the 12-db-per-octave system has a flatter frequency response for higher frequencies up to approximately the cutoff frequency Although the 24-db-per-octave characteristic has an even flatter response in this respect its resonant peak probably causes additional phase distortion that leads to a greater number of duration errors

Table I Percentages of records having QRS durations differing by more than 10 milliseconds from the durations of the wide-band recordings

Cutoff frequency (c p.s.)	Rolloff (db octave)		
	6	12	24
100	—	—	—
80	—	—	2
60	—	—	3 5
50	2	—	10
40	8	—	23
30	18	15	41
20	42	35	68

Table II is a summary of various other time intervals that were affected by high frequency performance. Except for Q waves where a larger number of records showed decreased durations, the majority of errors led to increased intervals or durations The inability to respond to low amplitude, short-duration Q waves is a result of recording with a very limited band width such as 20 or 30 c.p s. When this occurs th total QRS duration will appear to be shortened because of the lack of a Q wave

Q R, and S amplitude errors are tabulated in Table III Each three-number entry in the table represents the percentage of records which exhibited errors greater than 0 05 0 10 or 0.20 millivolt respec

Table II Errors in Q-wave duration R peak time and P R and Q-T intervals

Cutoff frequency ( )	Roll off (db octave)	Q duration	R peak time	P R interval	Q-T interval
100	6	—	—	—	—
	12	—	—	—	—
	24	—	—	—	—
80	6	—	—	—	—
	12		2	—	—
	24	—		—	—
60	6	—	2	—	—
	12	—	3 5	—	—
	24		2	—	—
50	6		2	—	—
	12	—	7	—	—
	24	—	7	—	—
40	6	—	8	—	—
	12	—	7	—	—
	24	3 5	22	—	—
30	6	5	27	3 5	2
	12	3 5	17	—	2
	24	8	50	5	7
20	6	12	43	12	12
	12	10	42	5	10
	24	20	68	22	17

*The number of records [illegible] percentages in which errors exceeded 10 milliseconds or 20 per cent, whichever was greater are tabulated Both [illegible] and decreased durations are totaled.

Table III Errors of peak amplitudes of Q R and S waves greater than 0 05 0 10 and 0.20 mv

Cutoff frequency ( )	Roll off (db octave)	Q		R		S	
		Increased	Decreased	Increased	Decreased	Increased	Decreased
100	6	0-0-0	6-0-0	0-0-0	29 2-0	0-0-0	10-2-0
	12	0 0 0	4 0-0	0-0-0	13 2-0	0-0-0	9-0 0
	24	2 0-0	2 2 0	2 0-0	47 11-0	4-0-0	9-0-0
80	6	0 0-0	7 0-0	0-0-0	39-13-0	0-0-0	7-0-0
	12	0-0-0	2 C-0	0-0-0	27 7-0	2-0-0	9-0-0
	4	9 0 0	5-2-0	0 0-0	52 14 2	11 2-0	2-0-0
60	6	C-0-0	13 2 0	0 0-0	44 15-2	0-0-0	10-6-0
	12	C 0-0	9 2 2	0-0 0	35-9-0	2-0-2	18-4-0
	24	C-0-0	11 2 2	2 0 0	44 16-6	12-4-4	7 2 0
50	6	0-0 0	13-0-0	0-0-0	55 11-4	0-0-0	16-4-0
	12	0-0 0	8-0-0	0 0 0	53 14 2	2-0 0	6-4-0
	24	2 0 0	12 0-0	2-0-0	61 12-4	22 2-0	6-2-0
40	6	0 0-0	17 4 0	0 0-0	75 37-4	0-0-0	19-4-0
	12	0 0-0	18 0 0	0 0 0	70 18-6	2-0 0	11 2-0
	24	0 C 0	16-9-0	2-0 0	57 18-6	32-4 2	4-0-0
30	6	0 0 0	24 8-2	0 0 0	78 52 13	0-0 0	30 15-4
	12	0 0 0	18 0-0	0 0 0	75 37-6	2 2-0	14 10 2
	24	0 0 0	29 8 0	4 0 0	55-33 8	43 18 2	2-0-0
20	6	0 0 0	34 15 2	0 0-0	77 74 30	2 0 0	28 10 4
	12	2 0-0	44 6-2	0-0-0	87 72 26	6-2 2	21 12 2
	24	2-0 0	46 26-6	2-0-0	87-69-43	54 30-6	8 2-0

The three numbers [illegible] each entry represent [illegible] percentages of records having amplitudes differing by more than 05 10 and 0 20 millivolt respectively from [illegible] values of the wide band recordings.

*Table IV The generation and disappearance of Q and S waves**

Cutoff frequency (c.p.s.)	Rolloff (db/octave)	Q waves		S waves	
		Generated	Missed	Generated	Missed
100	6	—	—	—	—
	12	—	—	—	—
	24	—	—	—	—
80	6	—	—	—	—
	12	—	—	—	—
	24	—	—	2	—
60	6	—	—	—	—
	12	—	—	—	—
	24	—	—	3.5	—
50	6	—	—	—	2
	12	—	—	—	—
	24	—	—	5	—
40	6	—	—	—	3.5
	12	—	—	—	—
	24	—	2	7	—
30	6	—	3.5	—	7
	12	—	2	—	2
	24	—	2	17	2
20	6	—	7	3.5	8
	12	—	5	—	8
	24	—	8	27	5

*Lists the records, in percentages, in which Q and S waves of minimum magnitude of [illegible] millivolt were either newly generated or completely missed.

*Table V Errors in amplitude ratios of Q/R and R/S**

Cutoff frequency (c.p.s.)	Rolloff (db/octave)	Q/R			R/S		
		Increased	Decreased	Total	Increased	Decreased	Total
100	6	7	3.5	10.5	7	7	14
	12	0	3.5	3.5	9	2	11
	24	7	2	9	9	7	16
80	6	7	5.5	12.5	2	11	13
	12	3.5	2	5.5	7	3.5	10.5
	24	9	3.5	12.5	2	14	16
60	6	5.5	5.5	11	7	3.5	10.5
	12	2	7	9	18	7	25
	24	2	7	9	11	18	29
50	6	5.5	9	14.5	12.5	7	19.5
	12	9	5.5	14.5	3.5	12.5	16
	24	11	7	18	3.5	25	28.5
40	6	9	7	16	12.5	5.5	18
	12	7	11	18	12.5	14	26.5
	24	12.5	18	20.5	5.5	38	43.5
30	6	14	29	43	29	7	36
	12	9	11	20	12.5	16	28.5
	24	7	25	32	2	44	46
20	6	7	25	32	27	7	34
	12	7	31	38	22	14	36
	24	5.5	42	47.5	3.5	65	68.5

*The number of records, in percentages, is listed in which Q/R and R/S errors greater than 10 per cent occurred.

tively The base line used for all measurements of amplitude was the beginning of Q It is again generally true that decreasing the cutoff frequency and increasing the rolloff results in a greater numbers of errors. R wave amplitudes were more often affected than were either Q or S waves, although errors in Q and S waves were not rare With few exceptions errors in Q and R waves generally resulted in decreased amplitudes however S-wave errors often resulted in increased amplitudes with the use of the 24-db-per-octave filter In a number of records Q and S waves were either generated or completely lost, as compared to the wide-band recordings. Table IV is a tabulation of the percentage of records in which this type of error was observed The criterion used for either the generation or disappearance of a wave was 0 05-millivolt amplitude that is any amplitude which was measured to be below 0 05 millivolt from the base line was classified as being indistinguishable from noise and therefore considered to be part of the base line



Fig 4 Oscilloscopic photographs of the X lead of patient Each of the seven photographs shows two wave forms simultaneously recorded The earlier one in time is the wide-band record and the other is the filtered record using the 24-db-per-octave filter The filtered records were recorded with high-frequency cutoffs of *(from the uppermost photograph downward)* 100 80, 60 50 40 30 and 20 c.p.s. Vertical and horizontal scales shown in upper left hand corner are 1.0 mv and 10 milliseconds respectively

Since Q/R and R/S ratios are often used in diagnostic interpretation the records in which the values of these ratios were altered by more than 10 per cent were selected Table V tabulates the percentage of records in which errors of this type appeared Q/R and R/S ratios were affected to about the same degree as were amplitudes only

Figs. 4 5 and 6 are examples of the distortions that can occur as the high frequency response of the recording system deteriorates The low pass filter used in these oscilloscope photographs was of the 24-db-per-octave type

Fig 4 represents the X lead of a patient As compared to the original wide-band recording the tracing taken with a cutoff frequency of 100 c.p.s. is not much different, although a slight increase in the S-wave amplitude can already be noticed (It is interesting to note that a phase shift *lag of approximately 2 milliseconds is present.)* As the cutoff frequency is lowered the S-wave distortion becomes more and more prominent At a cutoff frequency of 80 c.p.s. for example the S-wave amplitude has increased about 0 1 millivolt over the wide band recording

Fig 5 represents the Z lead of the same patient as in Fig 4 At a cutoff frequency of 100 c.p.s. the only noticeable distortion is the phase shift of the entire QRS complex. At 80 c.p.s. the R wave amplitude has increased by about 0 1 millivolt. This increase becomes greater as the cutoff frequency is lowered At 50 c p.s. and below a lowering of the Q-wave amplitude together with the production of an S wave can be seen The decrease in the Q-T interval is also apparent here because of the phase shift in the QRS complex which is almost nonexistent in the T wave. Since

the frequency content in the T wave itself usually does not extend beyond a few cycles, the high frequency characteristics of the recording device will rarely affect it.

Fig 6 represents the X lead of another patient. At a cutoff frequency of 100 c.p.s. there is no noticeable distortion except for the slight phase shift. However at a cutoff frequency of 60 c.p.s. there is a definite decrease in the R wave amplitude coupled with the production of an S wave where none existed before These two effects increase as the cutoff frequency is decreased The increase in QRS duration accompanying these effects is apparent

Discussion

It has been pointed out by Dower and co-workers[12] that direct writing electrocardiographs in present use generally behave as third-order low pass systems. That is, the high frequency response falls off with a slope of approximately 18 db per octave with no resonant peaks. However reference to Fig 1 of a previous paper by some of these same authors indicates that some direct writers had high-frequency characteristics that exhibited 12-db-per octave slopes and others had resonant peaks. Therefore it seemed to be appropriate to include such filter characteristics in the present study as being particularly relevant to presently available instruments. Although it is indeed difficult to design a heated-stylus direct writing instrument with a 6-db-per-octave rolloff this filter characteristic was selected for the present study in order to determine whether its use would result in an improvement in accuracy If desirable a 6-db-per-octave

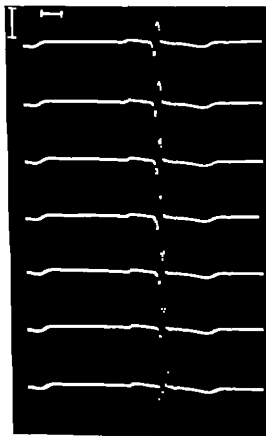


Fig 5 Oscilloscopic photographs of the Z lead of the same patient as in Fig 4. (For description, see legend to Fig 4.)

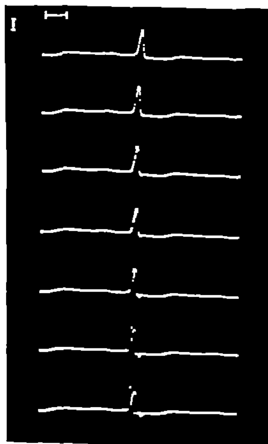


Fig 6 Oscilloscopic photographs of the X lead of another patient. (For description, see legend to Fig 4.)

characteristic could be obtained in a direct writer by using suitable electronic circuitry to compensate for the mechanical characteristics of the recording mechanism.

The interpretation of the results listed in the tables requires some explanation of the characteristics of the three types of frequency response curves shown in Fig. 1. In so far as amplitude distortion is concerned, the 24-db-per-octave system having the resonant peak will exhibit the least errors up to the cutoff frequency, whereas the 6-db-per-octave system will produce the largest amplitude attenuations. Above this frequency, however, the 24-db-per-octave system will produce greater amplitude attenuation than either of the other two systems and the 6-db-per-octave system will cause the smallest amplitude errors. On the other hand, phase shift effects will be greatest in the vicinity of the cutoff frequency for the system having the steepest rolloff, the 24-db-per-octave system, and least for the 6-db-per-octave system. Furthermore, because of the resonant peak and steep amplitude attenuation, the 24-db-per-octave system is more likely to give rise to artifacts, such as ringing.* Since the phase shift effects of the system will very likely show up as duration errors, the tabulation shown in Table I does demonstrate that this type of error is more easily produced by the 24-db-per-octave system. Even at a cutoff frequency of 80 c.p.s., for example, 2 per cent of the records were reproduced with QRS duration errors by the 24-db-per-octave system.

On the whole, amplitude errors in Q, R, and S waves appeared about as often no matter which of the three response characteristics was used. This is probably due to the amplitude attenuation effects of the three systems. Although the 6-db-per-octave system attenuates amplitudes below the cutoff frequency more than either of the other two systems, it has a better amplitude response above the cutoff frequency. Roughly, then, amplitude errors are more related to cutoff frequency than to rolloff characteristics. Table III presents a picture of the magnitude of the amplitude errors that may occur. It indicates that a significantly high percentage of errors can occur even at a cutoff frequency of 100 c.p.s. However, since a resolution of 0.05 millivolt in direct writers is debatable, it might be argued that a 100-c.p.s. response is satisfactory, since only one record showed an R wave error exceeding 0.10 millivolt with a 12-db-per-octave system.

The appearance and disappearance of Q and S waves is interesting. Table IV lists the percentages of records in which the low pass recording systems caused the loss or the generation of such waves. (For a wave to be recognized as present and distinct from the base line, an amplitude of at least 0.05 millivolt and a minimum duration of 10 milliseconds were used as the criteria.) Even at a cutoff frequency of 80 c.p.s., 2 per cent (actually one record) showed such an S-wave change with the 24-db-per-octave rolloff system.

Q/R and R/S ratios are often used to aid in the interpretation of infarctions and hypertrophies. Table V tabulates the percentage of records in which these ratios were altered by more than 10 per cent by the high frequency response characteristics of the recording system. Generally, these errors varied in a manner similar to Q, R, and S amplitude errors. As this table shows, it is difficult to predict in which direction these ratios will change. Often, for example, the R amplitude will decrease but the S amplitude will decrease by a different percentage, resulting in an increase or decrease in the R/S ratio. At 100 c.p.s., the number of records in which ratio errors occurred is still quite high. The best performing system (12-db-per-octave) resulted in a total error of over 14 per cent for Q/R and R/S ratios. Many of these errors, of course, would not necessarily cause a change in ECG interpretation; for example, a change in the R/S ratio from 4 to 7, a typical one, would not be diagnostically significant. However, recent work has indicated that Q/R ratios, for example, are more useful in the diagnostic recognition of myocardial infarctions than are measurements of Q duration or amplitude. Many of the changes that were observed in Q/R

*If a pulse input is applied to a filter having an amplitude response that is sharply cut off, the output pulse overshoots or oscillates with damped oscillations, [illegible] area of the pulse. This phenomenon is sometimes referred to as ringing.

measurements were in the area of 0.10 to 0.50 and therefore overlap the normal ranges for Q/R in orthogonal leads.

It appears then that duration errors and amplitude errors in excess of 0.10 millivolt can be largely avoided by recording with a cutoff frequency above 100 c.p.s. provided that no resonant peaks occur below this frequency. It also appears as though a 12-db-per-octave rolloff characteristic is slightly superior to a 6-db-per-octave rolloff. If an 18-db-per-octave rolloff were used as Dower and co-workers[1] have shown as being most representative of direct writers, the number of errors would perhaps have been reduced still further.

However, if the value of 0.05 millivolt is selected as the criterion for amplitude errors, a cutoff frequency of 100 Hz would be inadequate. Reference to Table III, for example, indicates that the best-performing system studied, the 12-db-per-octave system, produced errors in Q, R, and S amplitudes in 4, 13, and 9 per cent of the records, respectively. The requirement of a resolution of 0.05 millivolt is reasonable in view of the present trend in electrocardiography toward more quantitative results. The use of a frequency response significantly exceeding 100 Hz, probably about 200 Hz, is definitely an advantage in keeping amplitude errors below 0.05 millivolt.

Although this study did not include cutoff frequencies above 100 Hz, there would undoubtedly be an improvement if direct writers could perform well beyond this frequency. The majority of electrocardiographs presently in use employ a heated stylus as the recording device, and the capability of obtaining high-frequency performance above 100 Hz with such a design is doubtful. However, some direct writing electrocardiographs presently available employing designs other than the heated stylus are able to achieve high frequency performance of several hundred cycles and certainly should be recommended wherever higher fidelity is desirable.

Figs. 4, 5, and 6 help to explain why QRS durations appear to be affected much less than QRS amplitudes. Although phase shift becomes apparent even at a cutoff frequency of 100 c.p.s., the whole QRS complex shifts so that the beginning and the end of the complex get delayed by about the same amount. As an example, even in the production of an S wave, as in Fig. 4, the QRS duration increased by less than 10 milliseconds when a cutoff frequency of 50 c.p.s. was used.

Although the evidence does point to the desirability of recording with an upper cutoff frequency greater than 100 c.p.s.,* it should be kept in mind that the use of such a recording system will give rise to problems. In particular, one of the most common problems in the routine recording with direct writers is electromagnetic interference at the power-line frequency and its harmonics. Certainly, when recording is done with a cutoff frequency below 60 c.p.s., the interference from this source which appears on the tracing is less than if a system with a wider frequency response is used. Thus a higher cutoff frequency, although decreasing Q, R, and S amplitude errors in one sense, could actually result in greater errors because of the effect of the increased 60 c.p.s. and its harmonics on the tracing. Therefore, the use of a recording system of higher fidelity in terms of upper frequency response must be coupled with greater care in the recording techniques of grounding, application of electrodes, and shielding of the patient to reduce power-line interference.

Summary

The majority of direct writing electrocardiographs in present use have inadequate high-frequency response characteristics in that Q, R, and S amplitude errors will result when such systems are used for recording. In a study of 60 electrocardiographic waveforms, wide band (greater than 1,000 c.p.s.) recordings were compared with recordings using lower cutoff frequencies. Identical complexes were compared. In order to reduce Q, R, and S amplitude errors below 0.10 millivolt, a cutoff frequency greater than 100 c.p.s. is required.

Errors in the duration of QRS are less

*Since the preparation of this manuscript, the American Heart Association has prepared a revised set of recommendations for direct-writer performance in which a 100 Hz minimum frequency response is suggested.

affected unless the cutoff frequency is reduced to the vicinity of 60 c.p.s. Other time intervals such as Q-wave duration and P-R and Q-T intervals are affected in somewhat the same manner as QRS durations, and a small percentage of records exhibited errors in these durations even with a cutoff frequency of 80 c.p.s.

The use of direct writers having a cutoff frequency of at least 100 c.p.s. with no resonant peaks below this frequency is recommended as a minimum response. To reduce amplitude errors below 0.05 millivolt the use of a considerably greater cutoff frequency, perhaps 200 c.p.s., is recommended. It is also suggested that recording techniques need to be improved in order to take advantage of the higher frequency response because of the increased capability to respond to power line frequency interference.

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A rapid method for studying vascular patterns three dimensionally and histologically

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Many techniques are available for the gross demonstration of vascular patterns in organs and tissues. The use of injections of India ink[1-3] with subsequent clearing is perhaps the most common means of studying microcirculatory patterns. Various histologic procedures[4] have likewise contributed to our knowledge of the circulatory system. Both methods of study have advantages as well as inherent limitations. Injected and cleared specimens give a three-dimensional view of the microcirculation; however, the relationships of the blood vessels to adjacent tissue components are masked. Moreover, it is extremely difficult to distinguish between arterial and venous channels in these tissues. On the other hand, histologic sections do permit a detailed study of the relationship between the vessels and adjacent tissue but do not provide three-dimensional orientation of the angioarchitecture. It would be advantageous, therefore, to (1) combine these two methods of study so that the limitations of each are resolved, thus providing a more comprehensive study of microcirculatory patterns, and (2) to reduce the amount of time required for preparation of the tissues.

The purpose of this paper is to describe a rapid method of combining two routine procedures to study detailed vascular patterns in gross tissues (with a binocular dissecting microscope) and using the same specimen to confirm or study the relationships of blood vessels to tissue components after the preparation of histologic sections.

Materials and methods

Dogs, cats, hamsters, and rats were anesthetized with pentobarbital sodium. A 26-gauge needle was inserted through the body wall into the left ventricle. A 50-c.c. syringe, filled with warm (38°C.) heparinized Pelikan India ink,† was fitted over the needle, and the ink was slowly injected until the sclera, gums, and tongue became black. The amount of ink injected varied with the size of the animal: for dogs and cats, about 150 c.c., and for hamsters

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Fig. 1. A surface view of the second premolar tooth of a cat showing the vasculature of the pulp. Cleared in methyl benzoate. ×28.
Fig. 2. A histologic section of Fig. 1. Stained with hematoxylin and eosin. ×188.
Fig. 3. A surface view of the intramuscular vascular patterns in the sciatic nerve of a cat. Cleared in methyl benzoate. ×35.
Fig. 4. A histologic section of Fig. 3. Stained with hematoxylin and eosin. ×188.
Fig. 5. A surface view of the villi in the jejunum of a cat. Cleared in methyl benzoate. ×93.
Fig. 6. A histologic section of Fig. 5. Stained with hematoxylin and eosin. ×683.

and rats about 30 c.c The animals were then killed if necessary with an overdose of anesthetic and placed in a refrigerator until dissection could be conveniently performed (1 to 24 hours)

The diaphragm ribs, frontal bones, mandible gut, bladder pancreas, and sciatic nerves were removed from the animals and fixed in 10 per cent formalin All osseous material was placed in Decal for 6 hours (at 37°C and 20 inches mercury vacuum) prior to dehydration and clearing

The dissected tissues were dehydrated in three changes of acetone and cleared in one change of methyl benzoate (15 minutes each at 37°C and 20 inches mercury vacuum)

For study and photography the tissues were submerged in a Petri dish filled with methyl benzoate (because the tissues dried rapidly when exposed to air) We used a Leitz dissecting microscope at magnifications up to 216X A Leica III g 35 mm camera was attached to an Ipso 1/3 intermediate adapter and inserted into an ocular of the dissecting microscope.

After photography at varying depths of focus through the tissues the cleared specimens were placed directly into paraffin for 2½ hours at 57°C in a vacuum oven (20 inches mercury) blocked serially sectioned (7 to 10 microns) and stained with hematoxylin and eosin The histologic sections were then studied and the vascular patterns were correlated with photographs of the identical vessels previously studied in the cleared tissues.

Discussion

By introducing a heparinized biologic ink directly through the body wall into the left ventricle, the integrity of the animal is disturbed to a very small degree. Since the ink is injected into the ventricle the heart serves as the pumping mechanism to distribute the ink throughout the body The vascular patterns thus demonstrated should be more accurate representations of the normal circulation than those obtained by injecting ink after the animals have been killed or exposed to surgical trauma i.e., cannulating vessels.

It is not necessary to fix the tissues prior to dehydration and clearing We stored the tissues in 10 per cent formalin until it was convenient to resume the work at some later time

Since the injected tissues have already been dehydrated and cleared these steps may be eliminated from the histologic procedure and the tissues placed directly into paraffin It is also possible to make frozen sections of the cleared tissues if this is desired Some distortion was present in the histologic sections because of the rapidity of the technique however this was not considered to be significant since the relationships of the blood vessels to tissue components were not greatly altered Distortion of tissue may be reduced by using a graded series of alcohols or acetone during the dehydration of the tissues prior to clearing

Summary

A method has been described whereby specific vascular patterns can be studied three dimensionally in intact tissues photographed at varying depths of focus, and using the same specimen histologic sections quickly prepared to confirm the relationships of the blood vessels to tissue components which were previously masked in the cleared specimens.

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Antiarrhythmic actions of propranolol in the dog heart lung preparation

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Several beta adrenergic blocking agents have been reported to suppress adrenergically induced arrhythmias in experimental animals [19] and in man [11,14] Many of these agents have also been found to inhibit cardiac arrhythmias produced by digitalis glycosides [4] although recent experiments carried out in several laboratories have suggested a different mode of action in the blockade of digitalis induced arrhythmias On the basis of their antiarrhythmic actions the beta-adrenergic blocking agents may be divided into two categories (a) those which suppress adrenergically induced as well as digitalis-induced arrhythmias, and include dichloroisoproterenol (DCI) pronethalol Ko 592 (1-(3 methylphenoxy) 2 hydroxy 3-isopropylaminopropane)[22] and drobutamine[26] and (b) those which antagonize adrenergically induced arrhythmias selectively such as INPEA (N isopropyl p-nitrophenyl ethanolamine) [27] MJ 1999 (4-(2 isopropylamino-1 hydroxyethyl) methanesulfonanilide) [21,27] and INI (paramethyl isoproterenol)

More recently propranolol an analogue of pronethalol has been shown to suppress various types of cardiac arrhythmias.[19-21,23] The present study was undertaken to investigate further the antiarrhythmic action of propranolol in the dog heart lung preparation

Methods

Heart-lung preparation (*HLP*) Dogs of either sex weighing between 11 and 18 kilograms were anesthetized with 30 mg per kilogram of sodium pentobarbital intravenously The HLP was set up according to a modification of the method of Knowlton and Starling The technique of producing arrhythmias has already been described in detail [22] Briefly the thorax was opened by a midline incision and the blood vessels were cannulated in the usual manner The aortic pressure was kept between 90 and 110 mm Hg at the beginning of the HLP by adjusting a fixed (screw-clamp) type of resistance instead of the usual Starling type of variable resistance The cardiac output was measured with an extracorporeal flow probe (Medicon model FM-6R electromagnetic flowmeter) which provides an excellent means of continuous and reliable record of the cardiac output on the polygraph The external circuit of the HLP is shown in Fig 1

Adrenergically induced arrhythmias were

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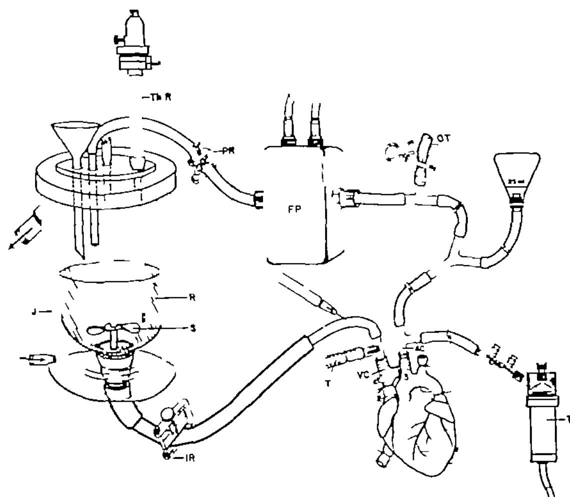


Fig. 1. Schematic diagram of the external circuit of the heart-lung preparation. *1* Inferior vena cava. *2* Superior vena cava. *3* Brachiocephalic trunk. *4* Descending aorta. *AC* Arterial cannula. *VC*, Venous cannula. *T* Thermometer. *T* Statham P23AA transducer. *OT* Outlet tubing. *FP* Flow probe sensor. *PR*, Screw-clamp type of "fixed" peripheral resistance. *ThR*, Thermoregulator. *R*, Blood reservoir 1,000-ml. capacity. *S* Stirrer. *J* Outer jacket surrounding the reservoir. The position of syringe indicates the approximate site of administration of the drug to the heart-lung preparation.

produced by exposing the HLP to 1 per cent halothane for 60 seconds followed by 50 μg of epinephrine. The effect of halothane-epinephrine combination on cardiac rhythm was observed for 10 to 25 seconds. During the next 30 to 60 seconds the aortic pressure was gradually elevated mechanically (by tightening the screw-clamp serving as the outflow resistance) until ventricular arrhythmias appeared or until no further elevation in the aortic pressure could be obtained. After the arrhythmia had been recorded for 60 to 90 seconds, the aortic pressure was gradually lowered to the original level and halothane was discontinued. Since adrenergically induced arrhythmias could not be reproduced in a given HLP,[20] the effect of propranolol was evaluated on the basis of group comparison in which the incidence and severity of arrhythmias in HLP pretreated with the blocking agent were compared with those obtained in the control group.

Ouabain-induced ventricular tachycardia was elicited in the HLP by injecting an initial loading dose of 40 μg followed 20 minutes later by 20 μg and thereafter by 10 μg every 10 minutes until a persistent ventricular tachycardia was produced. Propranolol was administered by a continuous

infusion (0.5 mg. per minute) 5 minutes after the ventricular tachycardia was established.

Results

Adrenergically induced arrhythmias. The results in 11 control experiments are shown in Table I. Prior to the mechanical elevation of the aortic pressure, ventricular fibrillation was produced in 3 experiments and only a few premature ventricular contractions were produced in 2 experiments. Additional mechanical elevation of the aortic pressure produced a multifocal ventricular tachycardia in 7 of 8 experiments.

When administered by a slow infusion (0.5 mg. over a period of 2 minutes) to the HLP, propranolol produced a significant (p < .05 calculated by paired analysis) decrease in the cardiac output from 906 ± 11 to 813 ± 31 ml. per minute, and heart rate from 184 ± 9 to 154 ± 4 beats per minute in the HLP. Pretreatment with propranolol effectively prevented the adrenergically induced arrhythmias in the HLP (Table II). Thus, cardiac irregularities were not seen in any of the preparations prior to, and a bigeminal rhythm was seen in only 1 experiment after, the mechanical elevation of the aortic pressure in the HLP pretreated with 0.5 mg. of propranolol. Although an elevated level of aortic pressure is essential for the genesis of adrenergically induced multifocal ventricular tachycardia,[22] the antiarrhythmic effect of propranolol in these experiments does not appear to be due to a lack of elevation of aortic pressure. Indeed, the maximum levels of aortic pressure at which the arrhythmias failed to appear were approximately the same prior to and significantly higher after mechanical elevation of the propranolol series as compared to the control preparations (Table I and II). In the dose administered, propranolol also inhibited significantly (Table III) the increase in heart rate and cardiac output produced by epinephrine, thus indicating an effective beta adrenergic blockade in the dose employed.

Ouabain-induced ventricular tachycardia in the HLP. The mean duration of ventricular tachycardia produced by ouabain was found to be 116 ± 6.6 minutes (range 90-140) in 6 control experiments.[22] The effect of propranolol (infused at a rate of 0.5 mg. per minute) on the ouabain-induced

Table I. Effect of epinephrine (50 μg) in dog heart-lung preparation sensitized with 1 per cent halothane (control experiments)

Experiment number	Prior to mechanical elevation of pressure: Type of arrhythmia	Prior to mechanical elevation of pressure: Maximal aortic pressure level (mm. Hg)	After mechanical elevation of aortic pressure: Type of arrhythmia	After mechanical elevation of aortic pressure: Aortic pressure level needed for arrhythmias (mm. Hg)
1	None	150	Multifocal VT	185
2.	VF	145	—	—
3.	Few VPC	165	Multifocal VT	190
4	None	180	Multifocal VT	190
5	None	142	Multifocal VT	175
6.	VF	155	—	—
7	None	153	Multifocal VT	190
8.	Few VPC	150	Multifocal VT	170
9	None	160	None	Up to 180
10.	VF	150	—	—
11	None	160	Multifocal VT	205
Total 11	5/11	Mean = 155 ± 3	7/8	Mean = 18[illegible] ± 3

*[illegible] experiment No. 9.
VF, Ventricular fibrillation; VT, Ventricular tachycardia; VPC, Ventricular premature contraction.

Table II Effect of pretreatment with propranolol (0.5 mg) on the action of epinephrine (50 μg) in dog heart-lung preparation sensitized with 1 per cent halothane

Experiment number	Prior to mechanical elevation of aortic pressure		After mechanical elevation of aortic pressure	
	Type of arrhythmia	Maximal aortic pressure level (mm. Hg)	Type of arrhythmia	Maximal aortic pressure level (mm. Hg)
1.	None	150	None	165
2.	None	130	None	240
3.	None	120	None	200
4	None	185	Bigeminy	260
5	None	160	None	280
Total 5	0/5	Mean = 149 ± 11	1/5	Mean = 229 ± 7

Table III Effect of epinephrine (50 μg) on heart rate and cardiac output in heart-lung preparation

Pretreatment	Number of experiments	Mean heart rate (beats/min. ± S.E.)			Mean cardiac output (ml./min. ± S.E.)		
		Before	After	Mean increase	Before	After	Mean increase
None (control)	7	147 ± 6	225 ± 12	79 ± 14	809 ± 58	1291 ± 72	482 ± 26
Propranolol (0.5 mg)	5	154 ± 4	182 ± 4	28 ± 9 p < .02	813 ± 31	11.6 ± 31	313 ± 38 p < .005

Prior to mechanical elevation of aortic pressure, sensitized with 1 per cent halothane. value calculated by group comparison.

Table IV Effect of propranolol on ouabain induced ventricular tachycardia in dog heart-lung preparation

Experiment number	Control heart rate (beats/min.)	Total dose of ouabain (μg)	Heart rate during VT (beats/min.)	Total dose of propranolol needed to suppress VT (mg)	Heart rate after propranolol (beats/min.)
1	140	70	200	13	116
2.	140	70	170	6	124
3.	100	70	190	11.5	120
4	160	70	180	9 0	144
5.	140	70	150	24.5	116
Total 5	136 ± 3	70	178 ± 5	9 87 ± 1 5	124 ± 5

*Excluding Experiment No. 3, in which only partial suppression of ventricular tachycardia was produced by propranolol.
VT Ventricular tachycardia

arrhythmia was investigated in a group of 5 preparations. A mean dose of 9.5 mg (range 6-13 mg) was needed to provide a complete restoration of the normal sinus rhythm in 4 experiments. Only partial suppression of the ventricular tachycardia by a total dose of 25 mg of propranolol could be obtained in the remaining HLH (Table IV).

Discussion

The results obtained in the present study clearly demonstrate that propranolol effectively blocked the arrhythmias induced by epinephrine as well as ouabain, although the dose needed to prevent adrenergically induced arrhythmias was much smaller than that needed to control ouabain-induced ventricular tachycardia. Similar results in intact animals were recently reported by Lucchesi and associates,[illegible] who found that a dose of 0.5 mg per kilogram prevented adrenergically induced arrhythmias and that a dose of 6.1 mg per kilogram was required to terminate ouabain-induced arrhythmias. The data obtained in the present study also demonstrate that propranolol is more effective than pronethalol in suppressing both epinephrine-induced and ouabain-induced arrhythmias. In previous studies we found that a dose of 10 to 15 mg of pronethalol was needed to prevent adrenergically induced arrhythmias in the HLH as compared to the 0.5-mg dose of propranolol in the present experiments. We also reported that pronethalol in doses up to 30 mg restored a normal sinus rhythm in only 1 of 6 preparations receiving toxic doses of ouabain, whereas a mean dose of 9.5 mg of propranolol restored a normal sinus rhythm in 4 of 5 HLH. A similar difference in the antiarrhythmic activity of pronethalol and propranolol has been reported by other investigators in intact animals.[illegible] Benfey and Varma[4] however did not find any difference between the activity of pronethalol and that of propranolol against ouabain intoxication in guinea pigs.

The present data also demonstrate that propranolol belongs to the group of beta adrenergic blocking agents which suppress both adrenergically induced and digitalis-induced arrhythmias. Moreover, as with other drugs in this group, the dose of pronethalol needed to suppress the latter type of arrhythmias is much larger than the dose necessary to prevent adrenergically induced arrhythmias or to produce beta receptor blockade. It is also evident that, as in the case of other beta adrenergic blocking agents,[illegible] suppression of ouabain-induced arrhythmias by propranolol involves a mechanism other than beta receptor blockade. Indeed, both pronethalol and propranolol have been demonstrated to exert quinidine-like actions on the refractory period and excitability of the myocardium. Like other well-known antiarrhythmic agents, both pronethalol and propranolol greatly reduced the rate of rise and the upshoot of the action potential without producing any change in the resting membrane potential in the rabbit atrial muscle. However, it is possible that such an effect on the electrical activity of the myocardium is due to a powerful local anesthetic effect exerted by both pronethalol and propranolol.[illegible] It would be interesting to know whether a similar effect on the action potential is exerted by other beta adrenergic blocking agents devoid of local anesthetic activity.

Finally, it seems to be appropriate to consider some of the possible mechanisms by which the adrenergically induced arrhythmias in the HLH are suppressed by propranolol. In this preparation the epinephrine-induced ventricular tachycardia was precipitated only when an additional stress was applied to the myocardium in the form of a mechanical elevation of the outflow resistance. Thus it is possible that propranolol antagonized such arrhythmias not only by blocking the beta effect of epinephrine but also by interfering with the direct (or indirect) deleterious effects of an abnormally high outflow resistance. The latter may include either one or both of the following effects: (1) an increased myocardial oxygen consumption (and a decreased myocardial efficiency)[illegible] resulting in a relative ischemia of the muscle fibers and (2) an increased rate of discharge of the potential ectopic pacemakers in the Purkinje fibers as a result of stretch of the myocardium.[illegible] Although recent evidence suggests that propranolol did indeed reduce the myocardial oxygen consumption during rest and exercise[illegible] and that it pre-

vented the increase in the rate of discharge of action potentials in the Purkinje fibers during stretch further experiments will be necessary to confirm the role of these actions in the over all antiarrhythmic activity of propranolol against epinephrine induced ventricular tachycardia in the HLP

Summary

The antiarrhythmic activity of propranolol a beta adrenergic blocking agent was investigated against epinephrine induced and ouabain induced ventricular tachycardia in the dog heart lung preparation Propranolol, in a 0 5-mg dose effectively blocked the myocardial stimulant and arrhythmogenic actions of epinephrine, although an average dose of 9 5 mg was needed to suppress ouabain induced ventricular tachycardia in this preparation Propranolol belongs to the category of beta-adrenergic blocking agents which suppress both adrenergically induced and ouabain induced arrhythmias, and as with other drugs in this group the mechanism of suppression of the two types of arrhythmias appears to be different

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The attenuation by reserpine or guanethidine of the cutaneous vasoconstriction caused by tobacco smoking

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Tobacco smoking and nicotine lead to vasoconstriction of the cutaneous blood vessels and to an increase in blood flow in skeletal muscle capillaries. The mechanism of action of tobacco smoking and nicotine on the peripheral vasculature is not entirely clear. Nicotine in small doses is considered to cause stimulation of the sympathetic nervous system. The role of the release of catecholamines from the adrenal medulla in eliciting cutaneous vasoconstriction during tobacco smoking (or nicotine in comparable doses) is not known. Epinephrine released from the adrenal medulla would be capable of decreasing blood flow in the skin and of increasing blood flow in skeletal muscle.

The present study was designed to investigate, by administration of catecholamine-depleting agents, the role of sympathetic nerves and of circulating catecholamines on the cutaneous vasoconstriction produced during cigarette smoking in normal subjects. A second objective of this study was to determine whether these agents would be effective in attenuating the cutaneous vasoconstriction caused by cigarette smoking for possible therapeutic use in patients with vascular disease who refuse to stop smoking.

Methods

Total blood flow in the foot was measured by venous occlusion plethysmography on lightly clothed subjects lying in the supine position. The leg was elevated in order to maintain the heel approximately at heart level. The foot was enclosed in a plethysmograph filled with water at a temperature of 89.6 F; the temperature of the water was carefully maintained within a range of 1°F. The technique for enclosing the limb in the water plethysmograph was previously described in detail. The level of water within the plethysmograph was 10 cm. above the foot. A pneumatic cuff 8 cm. wide was placed on the ankle proximal to the plethysmograph. Inflation of this cuff produced the venous occlusion necessary to measure blood flow. The lowest venous occlusion pressure required to obtain the maximum rate of increase in the volume of the foot was determined at the beginning of each experiment and averaged 42 mm. Hg. Fluctuations in the level of water in the plethysmograph were

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increase in vascular resistance in the foot during the pre-drug smoking tests were also compared with similar data for the guanethidine test (Fig. 2). Blood flow in the foot decreased 38 per cent in the pre-drug test compared to [illegible] decrease of only 15 per cent in the guanethidine test, a significant difference. The smaller per cent increase in vascular resistance in the foot during the ingestion of guanethidine compared to that in the pre-drug studies (36 vs [illegible]5 per cent) was also significant.

Resting blood pressure in the pre-drug studies averaged [illegible]8 [illegible] and decreased to 82 [illegible] 13 mm Hg during the administration of guanethidine (p [illegible] .01). Pulse rate in the pre-drug test averaged 5[illegible] ± 3.7 and [illegible] 6[illegible] ± 15.1 beats per minute during the administration of guanethidine (p < .05).

In all 8 subjects the average mean [illegible] rise [illegible] blood pressure on standing was 5 [illegible] 5 mm Hg; during the administration of guanethidine no subject showed a rise in blood pressure, and the average fall was [illegible] 8.5 mm Hg. All subjects showed a [illegible] overshoot of systolic blood pressure after the Valsalva maneuver which averaged 21 ± 6.6 mm Hg, whereas during the administration of guanethidine only 3 subjects showed a systolic overshoot (an attenuated one), and there was an average decrease in systolic blood pressure of 2 ± 7.6 mm Hg (p < 0.001). Before ingestion of the drug the subjects had an average rise in systolic blood pressure of 19 ± 1[illegible].5 mm Hg after exercise. During the administration of guanethidine no subject had a rise in systolic blood pressure after exercise; there was an average decrease of 32 ± 3.4 mm Hg. Seven of the 8 subjects experienced dizziness on standing or during exercise, 6 had diarrhea, 2 had nasal congestion, and 2 were generally tired.

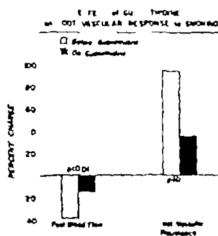


Fig. 2. Per cent decrease in blood flow and increase in vascular resistance in the foot during the pre-drug smoking tests (*white bars*) are compared with similar data for the guanethidine test (*black bars*). The probability value was obtained as for Fig. 1.

Discussion

In the present study cigarette smoking produced a significant decrease in blood flow and an increase in vascular resistance in the foot. This cutaneous vasoconstrictor effect of tobacco smoking has been documented by several investigators. In about 50 per cent of people smoking has been reported to diminish the increase in blood flow in the foot (called *reactive hyperemia*) which follows a period of arterial occlusion. Experiments on patients with sympathectomized limbs showed that the decrease in reactive hyperemia was mediated through the sympathetic nervous system. Studies are not available on the effect of tobacco smoking on the chemically or surgically sympathectomized limb in the resting state. In the present study catecholamine-depleting agents markedly attenuated or blocked the effect of tobacco smoking on blood flow and vascular resistance in the foot. After the administration of reserpine for 3 weeks, cigarette smoking produced no significant changes in blood flow or vascular resistance in the foot. After the administration of guanethidine the increase in vascular resistance in the foot during cigarette smoking was significant; however, the per cent increase in vascular resistance during smoking was significantly smaller during the administration of guanethidine than in the pre-drug studies.

These results with catecholamine-depleting agents indicate that cigarette smoking produces its effect on the cutaneous vasculature mainly via the sympathetic nervous supply. Evidently the release of catecholamines from the adrenal

medulla is not an important factor in the cutaneous response. This is in agreement with the studies of Burn who demonstrated that the vasoconstrictor action of nicotine in the rabbit ear is due to the release of norepinephrine; pretreatment of rabbits with reserpine prevented the nicotine-induced vasoconstriction. Although nicotine may cause the release of catecholamines from the adrenal medulla, the evidence is unconvincing that circulating catecholamines are important in producing the cardiovascular effects caused by tobacco smoking in man.

All subjects had unequivocal side effects from reserpine and guanethidine. The significant decrease in pulse rate with both agents and the attenuation of the Valsalva maneuver overshoot, the postural hypotension, and the hypotensive effect of muscular exercise with guanethidine demonstrate that the drugs were inhibiting considerable activity of the sympathetic nervous system. However, the failure of the drugs to alter the responses of blood pressure and pulse rate to cigarette smoking may indicate that the effects of cigarette smoking on the heart were not attenuated.

Agents which block the sympathetic nervous system or deplete catecholamines from sympathetic nerve endings have been recommended in the treatment of peripheral vasospastic diseases, especially Raynaud's disease.[18] The present study indicates that reserpine or guanethidine may be used to attenuate the vasoconstrictive effects of cigarette smoking in patients with vascular disease who refuse to stop smoking. These drugs must be administered cautiously, however, since postural or postexercise hypotension could lead to myocardial or cerebral ischemia if arteriosclerosis is present in the vasculature of the heart or brain. It is possible that the agents would be effective in lower doses than those which were used in this study. However, the side effects produced by the drugs as used in this study could be an inducement for the patient to stop smoking. In the case of arterial occlusive disease it may be that smoking accelerates the disease by mechanisms other than vasoconstriction, so that the harmful effects of smoking would not be entirely prevented by these drugs.

Summary

The effect of reserpine and guanethidine on the vasoconstriction in the foot induced by smoking 2 cigarettes was studied in normal subjects. Large daily clinical doses of guanethidine or reserpine were given for 2 and 3 weeks, respectively. Blood flow in the foot was measured by venous-occlusion water plethysmography. A pre-drug (control) study was performed on each subject; cigarette smoking produced a significant decrease in blood flow and an increase in vascular resistance in the foot. A statistically significant attenuation of the vasoconstrictor response in the foot to cigarette smoking was found with both drugs, compared to the pre-drug studies. Subjects evidenced a depletion of catecholamines during administration of the agent, by a significant decrease in pulse rate, by postural hypotension, by hypotension after exercise, and by blockade or attenuation of the Valsalva overshoot.[17]

Since reserpine and guanethidine produced a marked attenuation of the cutaneous vasoconstrictor response to smoking, the conclusion is that cigarette smoking exerts its effects on the circulation in the skin via the sympathetic nerves and that the release of catecholamines from the adrenal medulla is not important. Patients with peripheral vascular disease who refuse to stop smoking may benefit from the use of catecholamine-depleting agents.

This study was performed with the valuable technical assistance of Mrs. Beverly Hall, R.N.

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Changes in myocardial threshold
Physiologic and pharmacologic factors in patients with implanted pacemakers

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The purpose of this report is to point out certain physiologic and pharmacologic factors which are capable of causing measurable changes in the threshold energy requirements of the human heart. These studies were made possible by the development of simple external methods for making repetitive measurements of myocardial threshold and interelectrode impedance in patients with implanted pacemakers of a certain type.†

Random determination of threshold after implantation of a pacemaker have demonstrated that myocardial threshold in the human being is not a static quantity. On the contrary, it is highly variable, subject to spontaneous changes as well as being significantly modified by certain common drugs. A rational application of threshold analysis to the clinical care of patients, or the development of pacemaker technology, required as a first step a systematic controlled investigation of factors capable of modifying threshold. Our experience to date suggests that several factors affect threshold in a predictable way. The most important of these are the physiologic acts of exercise, eating, and sleeping. Steroids, sympathomimetic agents, and infusions of sodium, potassium, and solutions of potassium and insulin in glucose also had pronounced effects on electrical excitation. In presenting our findings to date, we would like to stress the importance of monitoring the electrical threshold of the heart in patients who are being paced by artificial means. As technology improves and these patients survive for longer periods, the various biologic factors involved in maintaining sustained responsiveness of the myocardium may assume greater importance.

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Methods and materials

All patients in this study had complete heart block and permanently implanted artificial pacemakers of the type which permit external measurement of myocardial threshold. These measurements can be performed only with this type of pacemaker. Patients ranged in age from 22 to 84 years, with a mean age of 66 years. Six were males and 8 were females. Bipolar myocardial electrodes were used exclusively. Measurements of threshold were made by using a threshold analyzer, a digital electronic counter (Model 5230 Beckman Berkeley Timer), and a cardiac monitor. Details of the threshold analyzer are reported elsewhere. Briefly, this instrument allows control of the rate and suppression of the energy output of the implanted pacemaker by introducing an inductively coupled high-frequency signal which prevents the discharge of the output condenser.

To measure threshold with the threshold analyzer, the output of the implanted pacemaker is slowly reduced by placing an induction coil directly over the implanted pacemaker and capturing control of the implanted unit through signals coming from the threshold analyzer. We have arbitrarily defined threshold as the first point at which, with gradual reduction of pacemaker output, one or more stimuli of every ten fail to excite the heart, as detected by the absence of QRS complexes on the cardiac monitor. The energy output of the pacemaker at threshold can be accurately calculated by the pulse width initially and at threshold, as previously described. Threshold is measured at the inherent rate of the implanted pacemaker.

Interelectrode resistance can be measured by determination of pacemaker pulse width and rate, and by a comparison of these parameters with precalibrated values for the biologic range of interelectrode resistance.[1]

In order to be sure that measured changes in threshold were due to an administered agent and were not secondary to spontaneous physiologic changes, a set of strict criteria was established as follows: (1) The pacemaker must have been implanted for at least 3 months in order to provide adequate time for the threshold to stabilize. (2) Prior to and during the test, the patient may take no medications except that being tested. (3) Physical activity is limited. The patient is confined to bed throughout each test period but is not allowed to fall asleep. Distracting activities such as reading or knitting are encouraged. (4) All studies are performed in the fasting state. Water is allowed. During experiments which require more than 8 hours, a light meal is permitted. (5) Threshold must remain constant (less than a 5 per cent change) for a minimum of 30 minutes prior to the beginning of each experiment. Rarely is it necessary to wait as long as 2 hours before this stabilization occurs. (6) After maximal change in threshold due to the experimental procedure, the threshold level must return to within 10 per cent of the base-line level and remain there. (7) Administration of a drug cannot be made in a manner which itself might alter threshold. Intravenous medication which results in rapid changes is given through a needle inserted before the start of the test, with no demonstrated change in threshold due to venipuncture or after stabilization of the threshold for 30 minutes after insertion of the needle. (8) The patient must not have a competing sinus rhythm or multiple ectopic ventricular beats.

All thresholds were measured as a per cent of available pacemaker *energy* and changes due to drugs or physiologic activities were reported as the *maximum* per cent change from the base-line threshold. For example, if a patient's base-line threshold were 20 per cent (of available pacemaker energy) and the administration of a drug resulted in a maximal increase to 26 per cent, this would be reported as a 30 per cent (6/20 × 100) change in threshold. After administration of a drug, the frequency of measurements of threshold was determined by the speed of action of the drug, e.g., measurements were made every 5 minutes during an infusion of potassium, and every one-half hour after an injection of aldosterone.

A total of 95 tests was performed on 14 patients, each specific test being run on at least 3 different patients. Twenty-four

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tests were discarded because of nonconformity to the above-mentioned criteria.

Results

In all tests reported the variation of threshold was less than 5 per cent over a 30-90-minute control period preceding the test. In 16 patients threshold was observed under control conditions for 3 to 6 hours, with less than 10 per cent variation in all cases. Setting tolerance limits we could be 95 per cent confident that 95 per cent of normal cases change 16 per cent or less under control conditions. Thus, for any patient whose threshold varied less than 5 per cent for at least 30 minutes prior to testing a threshold change of greater than 16 per cent after an experimental procedure was highly significant. Changes in threshold are reported in Tables I-V as plus (+) or minus (−) representing maximal per cent increase or decrease from base line values.

A. Physiologic studies. Table I shows the results of three different physiologic tests. Sleep appeared to have a profound effect, and in this study resulted in significant ($p < .001$) threshold elevations of 30 to 40 per cent. With one exception eating also resulted in a significantly increased threshold ($p < .001$). The exception was a patient not kept at a basal level of activity. Physical activity, on the other hand caused a significant ($p < .001$) lowering of threshold.

B. Pharmacologic studies. Four classes of pharmacologic agents were tested: electrolytes, sympathomimetic agents, atropine, steroids, and other drugs commonly used in cardiac patients.

1. ELECTROLYTES. Sodium, potassium, calcium, dextrose, and a solution of 40 mEq. KCl plus 20 units of regular insulin in 1,000 ml. of 10 per cent dextrose in water were given in a total of eight different concentrations. The rate of infusion for each solution is given in Table II. NaCl (0.9 per cent) resulted in insignificant changes, whereas 3 per cent NaCl infused rapidly resulted in very significant ($p < .001$) increases in threshold (+56, +60, and +56 per cent). In each case the hypertonic saline also caused a marked decrease in interelectrode resistance. The solution of potassium and insulin in glucose caused significant ($p < .01$) rises in threshold (+17, +32, +30, and +13 per cent). Ten per cent dextrose in water had an insignificant effect, and the same was true of a standard solution of KCl in dextrose (40 mEq. of KCl in 1,000 ml. of 10 per cent dextrose in water). When potassium was infused in Ringer's solution, however, it always resulted in a decreased threshold. The equivalent concentration (40 mEq. of KCl in 1,000 ml. of Ringer's solution)

Table I. Physiologic threshold changes each measured in 5 patients

	Number of tests	Maximal per cent threshold change
Sleeping	5	+38, +36, +41, +36, +30
Eating	5	+21, +26, +42, 0, +31
Exercise	5	−18, −11, −37, −32, −29

Table II. Effect of electrolytes reported as maximal per cent change in threshold (changes of 16 per cent or greater are considered to be significant)

	Number of tests	Maximal per cent threshold change
Polarizing solution	4	+17, +32, +30, +13
10% Dextrose in water*	4	+15, 0, 0, +3
40 mEq. KCl in 1,000 ml. 10% D/W	4	+12, +12, 0, 0
40 mEq. KCl in 1,000 ml. Ringer solution	3	−4, −23, −13
50 mEq. KCl in 500 ml. Ringer solution	3	−20, −44, −20
0.9% NaCl	3	+7, 0, +5
3% NaCl†	3	+56, +60, +56
0.5 Gm. Calcium gluconate‡	4	+17, −15, 0, 0

*Intravenously 30 drops per minute.
†Intravenously 20 drops per minute.
‡Intravenously given over [illegible] minutes.

resulted in changes of −4, −13, and −23 per cent, whereas a more concentrated solution (50 mEq of KCl in 500 ml of Ringer solution) yielded more significant ($p < .05$) decreases (−20, 20, and −44 per cent) in 3 cases (see Fig. 1). Ten per cent calcium gluconate (0.5 Gm.) given intravenously over 5 minutes caused no consistent changes. In most cases in which electrolyte solutions did alter threshold, the changes seemed to be transient, reaching a peak and in some cases returning toward the baseline level before the administration of electrolytes was stopped.

2. SYMPATHOMIMETIC AGENTS AND ATROPINE. Table III shows the results of administration of epinephrine, isoproterenol, ephedrine, and atropine. Atropine had no consistent effect on threshold, whereas epinephrine and ephedrine lowered the threshold, the effect of epinephrine being more significant ($p < .05$). Isoproterenol given intravenously (1 mg. in 250 ml. of 5 per cent dextrose in water) caused ... in 2 of 3 cases, but in all 3 cases the threshold subsequently increased to +56, +80, and +31 per cent ($p < .01$).

3. STEROIDS. Three patients were given intravenous methylprednisolone and 3 patients were given aldosterone (see Table IV) with significant ($p < .01$) changes from the drugs. In addition 10 patients have been given oral prednisone under noncontrolled conditions and this drug always caused decreases in threshold.

Table III. Effect of sympathomimetic drugs and atropine

	No. of tests	Per cent change in threshold
Epinephrine 1:1000	4	14, 11, 30, 16
Ephedrine	3	31, 0, 16
Isoproterenol	3	+56, +80, +31
Atropine	3	0, +16, 0

[illegible]
[illegible]
[illegible] mg. in 250 ml. of 5 per cent dextrose in water, 50 drops per minute
[illegible] mg. intravenously
[illegible] threshold ... marked. ... Fig. [illegible]

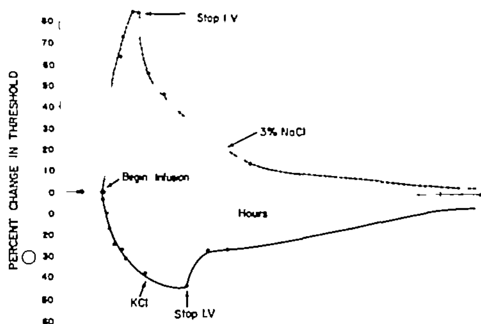


Fig. 1. Threshold changes after infusions of 3 per cent NaCl and KCl (50 mEq. in 500 ml. of Ringer solution). The infusions were in the same patient on different days. The 3 per cent NaCl was infused at a rate of 120 drops per minute, the KCl at 50 drops per minute. In each case threshold remained constant for at least 30 minutes prior to the infusion.

Table IV Effect of a potent mineralocorticoid and a potent glucocorticoid given to 3 patients

	Number of tests	Maximal per cent threshold change
d-Aldosterone 500 Gm., intravenously	3	+35 +39 +29
Methylprednisolone 40 mg intravenously	3	−21 −23 25

Table V Results of administration of digitalis (lanatoside C) procaine amide and morphine

	Number of tests	Maximal per cent threshold change
Digitalis*	3	+13, −9 0
Procaine amide†	3	0 +7 +37
Morphine‡	3	−8 −13 0

*Cedilanid 0.8 mg intravenously
†500 mg intravenously in 30 minutes
‡8 mg intramuscularly

the effect being related to dosage. The results to date indicate that glucocorticoids decrease and mineralocorticoids increase, the threshold. Fig 2 illustrates the opposite effects of these two steroids given to one of the patients.

4 PRONESTYL (PROCAINE AMIDE) CEDILANID (LANATOSIDE C) AND MORPHINE SULFATE. Table V shows the results of testing with these drugs. Procaine amide and lanatoside C had no significant effect The one rise of +37 per cent with procaine amide came 2 hours after administration of the drug there being no change in the acute period Morphine caused no significant changes in threshold

Discussion

It is generally thought that excitation of a single myocardial cell, or a syncytium of cells is a function of (1) the exciting stimulus (2) the resting membrane potential (3) membrane resistance and (4) the cellular threshold potential.[11] For excitation to occur the exciting stimulus must reduce the resting membrane potential to the level of the cellular threshold potential at which point the action potential begins Thus for a given pacemaker stimulus within certain limits a reduction of the resting membrane potential of the myocardial cells would theoretically reduce the threshold require-

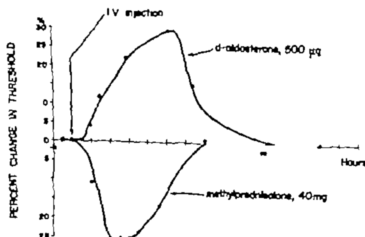


Fig. 2. Changes in threshold after intravenous administration of methylprednisolone and d-aldosterone, given to the same patient on different days.

ment An increase in the gap between cellular resting and thresh ll membrane potentials would in rease th my cardial thresh ld

Since all patient in thi stu ly ha l their pacemaker electrodes imp lanted directly into the myo rdium w um that the changes demon trat l were lue t effect on cell immediatel l ent t th elec tr les However t d lectr l were imp lanted leep ly ugh ther might also be in ll ti n l ffect mediated l y th Purkinj n l t k tem It i known that nt uk r m scle fibers are relatively insen tive t m ny ent that has n eff t on Purkinj t ue

Three pl y l rual les leeping eating l ver se pro luced significant changes n thresh ld We h l previou ly observe l in l n al ases f borderline high thresh ll p tient wh were not pa ng t r st wh uld be in luced to p l ld exercise l wering f thres hold s n l ry t phy ical a tivity i presum l t be lu t increased sympat th t t n l tion One patient who had be n resting omfortably had a sudden att k f a ut back pain and within 5 minutes her threshold dropped 57 per nt

The gn ficant elev ation f threshold accomp nied l y leeping or the eating of a large m al could be attributed to decreased sympath tic tone We have 2 patient who report having awakened with int rmitt nt pacing w th a return to normal pac ng after arising Th effects of exercise sleeping and eating account for most of the spontaneous changes in threshold observed For any patient these could result in swings of 50 per cent or more during the course of a day Although emotional factors may well have an ad ditional significant effect on threshold no attempt wa made in the present study to assess this element.

The results of infusion of electrolytes can be classified under three general head ings potassium sodium and calcium (see Table II) Electrolyte effects were often transient returning toward normal before cessation of the infusion in some cases.

Infusions of potassium and insulin in glucose resulted in significant rises in threshold whereas infusions of 10 per cent dextrose in water with or without po ta ium caused no significant effect It i known that in ulin increases the uptake of pota ium by cardiac muscle[1, 11] and our fin l ng are con istent with the hypo thesi that thresh ll i increased l y in cre ing the K K rati thereby in cre ing the resting membrane potential and the threshold stimulu requirement We interpret the lack of ignificant change in threshold in response t solutions of dextrose and pot ium without insulin to an absence of significant change in the K K ratio. Mea urement of serum po t ium during the infu ion showed in on tant ch nges which establi hed no trend Thi i imilar t the find ng of thers. [15]

In an attempt to increase K without a proporti nal increase in K we infused p ta ium in Ringer s solution (Fi 1) The result in Table II show significant decreases in threshold by this method upporting the pos ibility that the K K ratio was indeed decreased Walker and a sociates have reported increased re p on veness (decreased thresh ll) to an implanted pacemaker after the adminis tration of oral potassium the mechanism presumably being an increase in K in relation to K

The striking effect of concentrated solution of NaCl in ra ing threshold (see Table I) varies from report that the sodium ion ha no eff ct on cellular ex citability The high concentrations of NaCl used in thi study may have resulted in shifts in potassium The ancillary find ing of a marked lowering of interelectrode resistance[1] with 3 per cent saline is proba bly a result of increased conduction be tween the electrodes secondary to hyper tonicity of the extracellular medium It is conceivable that this shunts current pa t the myocardial cell thereby in creasing the stimulus necessary for exci tation

We found no consistent changes after the intravenous administration of 0 5 Gm of calcium gluconate but it is possible that larger doses might have had an ef fect.[7, 11, 8]

The results with standard clinical doses

Ki = Intracellular potassium. Ke = Extracellular potassium.

of the sympathomimetic agents epinephrine and ephedrine showed a lowering of myocardial threshold. Hoffman and Cranefield[7,22] state that epinephrine has very little effect on the resting membrane potential of dog or cat ventricular fibers but it may lower the threshold of Purkinje fibers by increasing the membrane threshold potential. It is conceivable therefore that the effect of sympathomimetic agents on the responsiveness to an implanted pacemaker may depend in part on how close the electrodes are to the Purkinje system. Isoproterenol infused rapidly (see Fig. 3) caused first, a lowering of threshold and then a marked elevation of threshold. This is similar to findings in dogs reported by Siebens and co-workers.[20] It is possible that this is a dose-related phenomenon and that a smaller dose would produce a persistently decreased threshold.

The finding that a glucocorticoid methylprednisolone significantly lowers threshold whereas a potent mineralocorticoid aldosterone significantly elevates threshold fits with the authors' clinical impression that glucocorticoids increase responsiveness to a pacemaker and mineralocorticoids have the opposite effect. We have monitored the thresholds of 10 patients treated with prednisone and have found a marked reduction of threshold in all of them.

The mode of action of steroids is uncertain. Perhaps steroids affect threshold because of their influence on the permeability of the cell membrane. If such were the case, one would have to assume opposing effects of glucocorticoids and mineralocorticoids at the cellular level with the former decreasing and the latter increasing the permeability to potassium. The final effect on threshold would then be mediated by an altered resting membrane potential. Modification of the sodium-potassium relationships could also result in alteration of the cellular threshold potential. Aber and Jones[21] report large inverted T waves and Q-T prolongation during treatment with glucocorticoids which findings they think support the concept that steroids interfere with the sodium-potassium pump across the cell membrane. Another explanation for the effect of steroids on threshold is their known potentiation of catecholamines.

In our studies, digitalis and quinidine caused no significant changes in threshold although variable effects have been reported from microelectrode studies.[22] One of our patients had multiple ectopic ventricular beats competing with his electronic pacemaker. The administration of procaine amide to this patient resulted in complete disappearance of the ectopic beats but it caused no change in the threshold to stimulation by the electronic pacemaker. This finding shows the disparity between automaticity and responsiveness to electrical stimulation.

This investigation has demonstrated

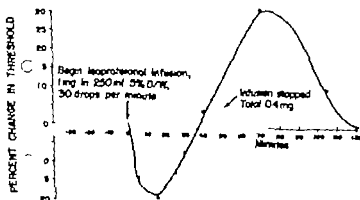


Fig. 3. Effect of intravenous isoproterenol, which caused initial decrease in threshold, and then elevation of threshold.

the lability of myocardial threshold in man and the susceptibility of threshold to manipulation by physiologic activities and pharmacologic agents. Although of uncertain clinical usefulness, these findings may be of benefit in cases in which it is desirable to alter responsiveness to electrical stimulation.

Summary

Seventy-one individual threshold studies were performed on 14 patients with implanted cardiac pacemakers.

Eating and sleeping raised myocardial threshold significantly, whereas exercise had a reverse effect. A solution of insulin and potassium in dextrose 3 per cent NaCl and Hyperton also increased threshold. Epinephrine, methylprednisolone, and potassium chloride in Ringer's solution lowered threshold. Isoproterenol caused an initial fall in threshold followed by a marked rise. No significant changes were demonstrated with 10 per cent dextrose, normal saline, calcium gluconate, lanatoside C, procaine amide, atropine, or morphine at those dosages that were arbitrarily chosen for this study.

The results demonstrate that myocardial threshold in man is labile and that it can be manipulated by physiologic activities and pharmacologic agents.

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Effects of ethanol and acetaldehyde on the heart

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Men have drunk alcohol in joy and in grief, alone and in groups, to celebrate and to forget, with hesitation and with compulsive habituation throughout recorded history. For many years physicians have known that patients consuming large amounts of alcohol frequently have heart disease. A resurgence of interest in this form of heart disease began with the recent studies of Evans, Brigden and Robinson, and Burch and Walsh, which stressed that the usual explanations blaming malnutrition and vitamin deficiency were too often incorrect or insufficient.

Despite considerable recent interest in this question, however, the reason that chronic alcoholics so often develop heart disease remains unclear. A paradox exists between the old clinical knowledge that chronic alcoholism is associated with myocardial insufficiency and most of the experimental evidence accumulated in the past, which indicates that alcohol has little direct effect on the cardiovascular system except in very high concentrations. With newer methodology there is now some clinical[8] and experimental[7] evidence which suggests that alcohol may alter the metabolism of the myocardial cell. Histochemical and electron microscopic studies of myocardium from patients dying with alcoholic cardiomyopathy have shown extensive morphologic changes, but whether these caused the heart to fail or whether they were due to the cardiac failure (and its therapy and complications) is unknown.

One may summarize present concepts about the pathogenesis of alcoholic cardiomyopathy as follows. There is little question that malnutrition and vitamin deficiency may lead to cardiac failure in the alcoholic patient who eats poorly, but this explains only a small portion of those with the disease. Since some alcoholics do not take care of themselves physically, they may be more susceptible to infectious diseases, and cardiac involvement by viruses may contribute to the problem, but in the absence of convincing evidence that such is often the case, this remains speculative. Deficient dietary intake of certain trace metals, particularly zinc and magnesium, may contribute to the pathogenesis of alcoholic cardiomyopathy. But the principal enigma in alcoholic cardiomyopathy concerns the patient who eats well, takes reasonably good care of himself, is not the victim of unusual viral or bacterial illnesses, yet just because he drinks too much eventually develops progressive cardiac enlargement and failure.

If continuing studies of this problem

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confirm that ingested ethyl alcohol in man has a *direct* noxious effect on the heart as some recent reports suggest, then the large volume of older information indicating insignificant direct cardiac effect will be refuted. However, the m tal h an l pathophysiologic consequen es of chronic alcoholism include more th n simply the direct action of ethanol. Ingested ethanol is rapidly metabolized t acetaldehyde and then to water and acetic acid. Acetaldehyde has been shown t have significant cardiovascular effect. In the present study we performed experiments t examine the effect of ethanol, acetaldehyde, and acetic acid on the sinus node and compared these with the effects of methanol, formaldehyde, and formic acid. Since the sinus node is composed of specialized myocardial cells, effects on it represent what may be anticipated (with few exceptions) as general cardiac effects. Furthermore, its function as the normal cardiac pacemaker gives it an essential role in determining how fast the heart beats.

Materials and methods

Sixty-five dogs were prepared for experiment as follows. After anesthesia with pentobarbital sodium (30 mg. per kilogram) the trachea was intubated for mechanical ventilation with room air. The chest was opened in the midline, the heart suspended in the pericardium, and the right coronary artery dissected free in the atrioventricular sulcus to isolate the branch to the sinus node. A small polyethylene cannula was introduced into the sinus node artery and ligated in place. Ligation of the canine sinus node artery has no significant effect on the rate of the sinus node[1] because of the extensive arterial anastomoses in that region.[19] A three-way stopcock attached to the proximal end of the cannula in the sinus node artery permitted injections into the artery and, between injections, the measurement of retrograde pressure. Other pressures routinely measured included those in the aorta (via a femoral artery) and the right atrium (via a jugular vein). Heart rate was constantly monitored by an instantaneous tachogram derived with an analog computer from successive R waves in the electrocardiogram. During constant recording of the tachogram and pressures at 0.25 mm. per second on a polygraph, the pulses and E.C.G. were monitored on an oscilloscope with a sweep speed of 50 mm. per second. Through a slave circuit a separate E.C.G. was recorded constantly at 25 mm. per second and collated with the master record. The right stellate ganglion was isolated within the thorax and stimulated with an electronic square-wave stimulator at 30 c.p.s., 1 millisecond impulses in 6-second trains at submaximal voltage.

Solutions for injection into the sinus node artery were prepared either in Ringer's solution or in fresh autogenous arterial blood as indicated. Ethanol, methanol, acetaldehyde, formaldehyde, acetic acid, and formic acid were so prepared. Of these, acetaldehyde presented a special problem because of its volatility at ordinary room temperature; for consistent preparation it was necessary to mix acetaldehyde in cold (about 6° C.) Ringer's solution or blood. Each injection into the sinus node was preceded by a control injection of either Ringer's solution or arterial blood. These injections were routinely of 2 ml. volume delivered from a hand syringe in 5 to 10 seconds. Any injection directly into the sinus node artery produces bradycardia which has been determined to be due most likely to physical distention of the sinus node artery.[20] After such injections there is routinely a brief postinjection acceleration which is due to local release of norepinephrine.[21] Atropine sulfate, 1 mg. per kilogram, was injected intravenously. Reserpine was administered intramuscularly, 0.5 mg. per kilogram for 2 days prior to an experiment. Propranolol* and l-norepinephrine bitartrate were prepared in Ringer's solution for intranodal injection.

Chronotropic effects of test solutions were interpreted relative to preceding control injections in each animal. Negative effects are reported only as they exceeded the control injection bradycardia in degree and duration. Positive effects are calculated as they exceeded the control degree and duration of postinjection acceleration. The effects of injections of acetaldehyde

*Supplied by Dr. A. Sahagian Edwards, Ayerst Laboratories, New York, N. Y.

which were all cold were compared routinely to control injections of the same temperature. The pulse amplitude in the ligated sinus node artery is due to atrial contraction[22] and was used together with the intra-atrial pulse as an indirect indicator of inotropic response.

Results

The results may be summarized by indicating that acetaldehyde was the only substance studied which produced an effect, except at very high concentrations. Ethanol had no significant chronotropic action except at 10 000 µg per milliliter (Fig 1)

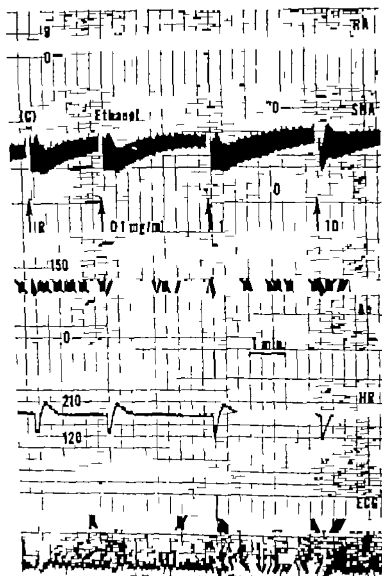


Fig 1 This experiment demonstrates the characteristic response t brief direct perfusion of the sinus node with ethanol. Bradycardia during injection and postinjection acceleration are the same after the control (*C*) injection of Ringer solution and af er 0.1 and 1 0 mg per milliliter of ethanol. Only with 10 mg. per milliliter of ethanol was there consistent negative chronotropic effect, here manifest by loss of the normal postinjection acceleration and slight prolongation of the injection bradycardia. Recordings in this and subsequent similar graphs are (*from above down*) right atrial pressure (*RA*) retrograde pressure in the cannulated ligated sinus node artery (*SNA*) aortic pressure (*A*) tachogram (*HR*) and electrocardiogram (*ECG*) The pressures re scaled in millimeters of mercury and HR in number of beats per minute. Recording paper speeds are indicated by horizontal-bar time references.

which is twice the level ever observed in man even in deepest drunkenness. The same was true of methanol. Acetic acid had an insignificant effect below concentrations of 100 µg per milliliter, at which level the pH of the test solution was 3. *Formic acid acted similarly.* Constituting the two acid in fresh autogenous arterial blood at the same concentrations lessened the acidity of the solution because of normal buffering mechanisms in blood and similarly reduced or eliminated the chronotropic effect. Formaldehyde had no significant effect below a concentration of 1,000 µg per milliliter (Fig. 2). The only cardiac effects observed with ethanol (16 dogs), methanol (4 dogs), acetic acid (10 dogs), formic acid (4 dogs), and formaldehyde (7 dogs) were depressive, slowing the sinus node and reducing the ampli

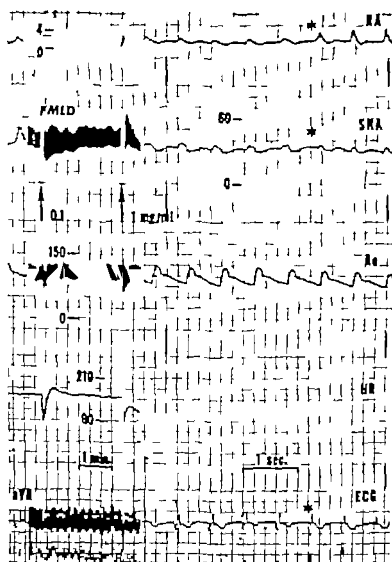


Fig. 2. *On brief direct perfusion of the sinus node, formaldehyde (FMLD) had no significant chronotropic action below concentrations of 1 mg. per milliliter,* and only negative action at that concentration. Here the transition from sinus rhythm to A-V nodal rhythm is demonstrated after 1 mg. per milliliter of FMLD had been injected into the sinus node artery. The point of transition is indicated by the asterisks. This effect lasted 2 minutes; recovery of sinus rhythm was attributable to the rapid removal of FMLD by flow from arterial anastomoses about the sinus node.

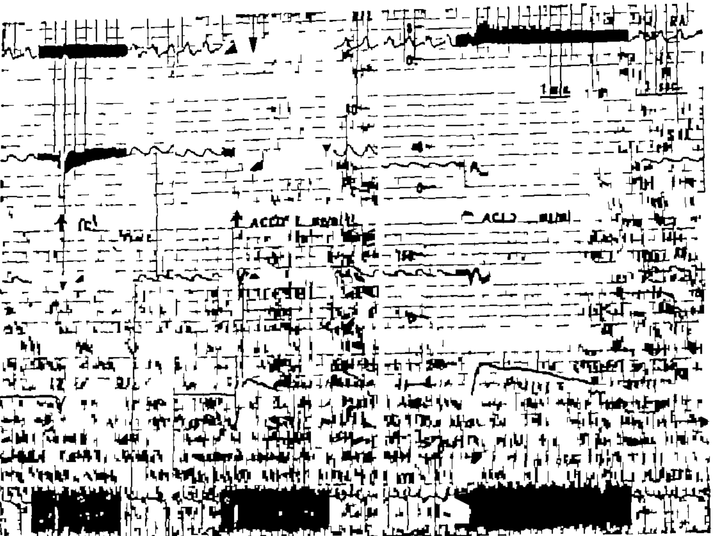


Fig. 3. The typical positive chronotropic action by acetaldehyde (*ACLD*) is demonstrated in this experiment. Compare the responses after 0.1 and 1.0 mg per milliliter of ACLD to that after the control injection of Ringer solution (*C*). Summary of results in similar experiments presented in Table I.

tude of atrial pulses, the latter representing a negative inotropic action. The depressive effects persisted after atropinization and reserpinization, indicating that they were not mediated by vagal stimulation and were not an antiadrenergic effect.

Acetaldehyde produced increasing degrees of acceleration of the sinus node with increasing test concentration, beginning with a significant but inconsistent effect at 10 µg per milliliter (Fig. 1 and Figs. 3 and 4). There was a concomitant increase in the amplitude of the pulse in the ligated sinus nodal artery and in the right atrium, indicating a positive inotropic action. Both the positive chronotropic and inotropic effects resembled the action of tyramine injected directly into the sinus node.[?] Serial injections of intranodal acetaldehyde, 1,000 µg per milliliter at 10 minute intervals (in 5 dogs), continued to produce maximal accelerative responses for 1 hour. Longer serial periods or shorter intervals between injections were associated with sinus arrest and periodic rhythm which most likely represented toxicity.

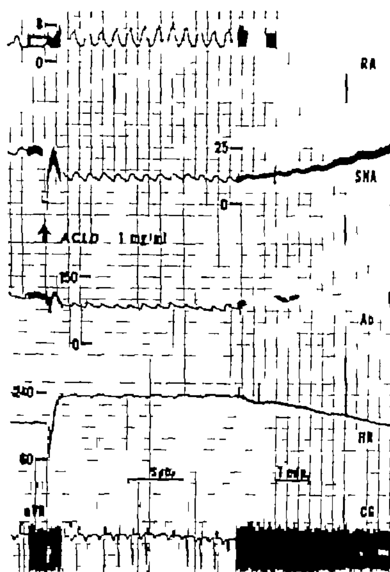


Fig. 4. During the effect of ACLD here the recording paper speed was accelerated to demonstrate that the rhythm remains of sinus origin in the ECG and the amplitude of A waves of the atrial pulse is increased.

Table I Sinus tachycardia from intranodal acetaldehyde in 16 dogs

	Concentration of acetaldehyde (μg/ml)		
	10	100	1,000
Maximum level of acceleration (beats/minute)	3 ± 11	23 ± 17	45 ± 12
Duration of acceleration (seconds)	Same as control	81 ± 51	311 ± 139

*Both the level and duration of acceleration are expressed only as they exceeded the response to control injections of Ringer solution in the same dog. Results for the 16 dogs are given as the arithmetic mean ± 1 S.D.

In the case of 3 dogs, acetaldehyde was freshly prepared in autogenous arterial blood and intranodal injections produced the same responses as did acetaldehyde prepared in Ringer's solution. Intravenous administration of acetaldehyde 1 mg per kilogram and less produced minor inconsistent effects but 10 mg per kilogram consistently produced both aortic hypertension and sinus tachycardia (Fig 5) as has been demonstrated by others.[38-41]

Aortic hypertension increased amplitude of atrial pulses, and sinus acceleration were all much diminished or absent after reserpinization in 4 dogs (Fig 6). The ac

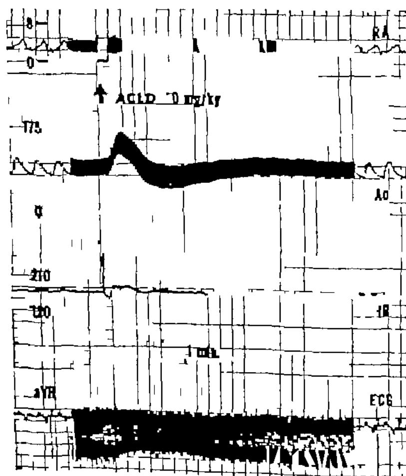


Fig. 5 An injection of acetaldehyde into the central venous circulation (right atrium) comparable to about 50 times the maximal volume given in the experiments with intranodal injection in Figs. 3 and 4 produces aortic hypertension and slight cardiac acceleration. The brief slowing during intra-atrial injection was due to the local effect of 10 ml. of cold test solution. Since the chronotropic action by this large volume of ACLD administered systemically is so much less than that by the much smaller volume perfused directly through the sinus node an extracardiac effect from recirculated ACLD is not likely to be a significant factor in the positive chronotropic response after intranodal ACLD

celerative response to acetaldehyde could not be restored with intranodal n r p nephrine in the reserpinized log lthough it can be with tyramin [21] it m y be n ted that intranodal norepinephrin lso f il to restore the response t timul ti n f the stellate ganglia n reserpiniz l log [21] The increased puls mplitud n l th sinus tachycardia were r ll r v rsibl in 4 dogs with intr l l propranol l (Fig 7) an l l k ked n mmedi tely ubsequent inject on of acetaldehyde In 3 of these 4 dogs responses to acetaldehyde were followed at 10-minute interval and returned to control levels of acceleration in 40 to 60 minutes which i the duration of action of propranolol in this experi mental prep ration Stimulation of the stellate ganglia in 3 dogs during the ac celerative effect of variou concentration of intran l l acetaldehyde produced either norm l or slightly reduced accelerative responses and increased atrial pulse ampli tudes (Fig 8) neither the positive chrono-

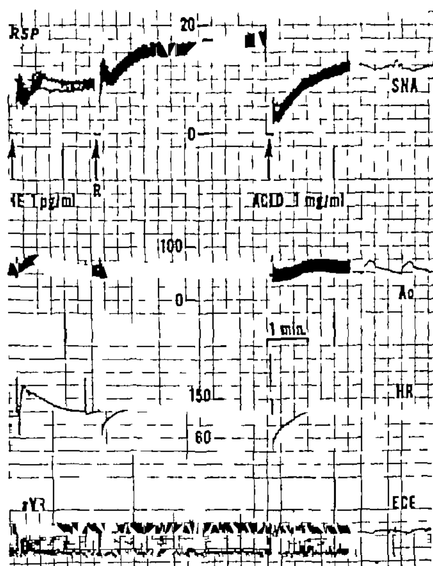


Fig 6 I this reserpinized dog (*RSP*) response t intranodal norepinephrine (*NE*) and control Ringer solution (*R*) is of the usual type, but 1 mg per milliliter of ACLD has no significa t chronotropic effect. The longer duration of i jection bradycardia after ACLD than after Ringer solution is due to a ash-l of NE from the catheter by the Ringer solution.

tropic nor inotropic neurogenic response was augmented by acetaldehyde. Sinus tachycardia from intranodal norepinephrine 0.05 and 0.1 μg per milliliter was not augmented by prior or concomitantly administered acetaldehyde. Maximal sinus acceleration from intranodal acetaldehyde was similar before and after intravenous atropinization in 3 dogs.

Discussion

Acetaldehyde clearly has profound direct effects on the heart. Cardiac stimulation occurred at levels which normally develop in man after ingestion of ethanol and resemble those observed after the experimental administration of acetaldehyde intravenously in human volunteers.[12] Concentrations of acetaldehyde after drinking in man may reach 10 μg per milliliter and with prior administration of disulfiram (Antabuse) can reach 100 μg per milliliter. Since both acetaldehyde and ethanol have a number of significant concomitant extracardiac effects[4, 10, 11] which may secondarily influence the heart, it is not surprising that physical findings, such as the blood pressure and heart rate, are so variable

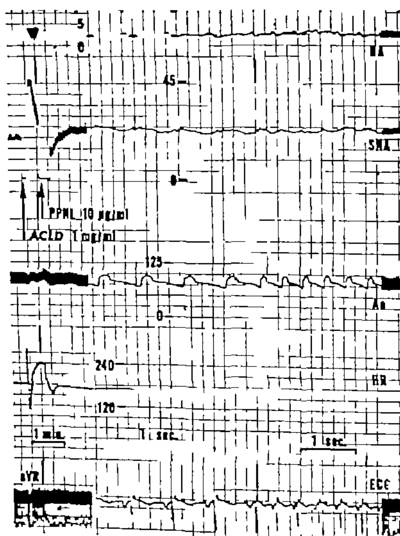


Fig. 7. Reversal of the effects of intranodal ACLD by intranodal propranolol (*PPNL*) is demonstrated in this experiment. The positive chronotropic effect is abolished, as apparent in the heart rate, and the positive inotropic response is abolished, as apparent by the reduction in right atrial pulse amplitude.

Fig. [illegible] The sinus tachycardia from stimulation of the right stellate ganglion (*RS*) was similar before (*left panel*) and during the positive chronotropic effect of 1 µg/ml ACLD. This makes it unlikely that sensitization to normally released (or normally present) norepinephrine is a significant factor in the positive chronotropic effect of ACLD.

in groups of alcoholic patients, as well as from one time to another in the same patient. Hypotension associated with the warm *flush* in acute alcoholism may counteract the hypertensive effect of acetaldehydemia. Tachycardia from acetaldehyde or secondarily from hypotension (or both) may be opposed by the direct noxious effect of ethanol on the heart or even by the toxicity of certain congeners occurring in some alcoholic beverages. In considering the mechanism of the ultimate cardiovascular effects of ethanol one must begin with an appreciation of the complexity of the factors involved. Since recent reviews have discussed the physiologic responses to ethanol and the many possible contributing factors in the pathogenesis of alcoholic cardiomyopathy,[2,3,5-34] this discussion will concentrate on the actions of acetaldehyde.

The possible role of acetaldehyde in the net effects of chronic alcoholism has been investigated by a number of workers, but primarily relative to *neurologic* effects and especially after disulfiram, which inhibits the degradation of acetaldehyde.[35] When one is considering the potential role of acetaldehyde in the genesis of alcoholic cardiomyopathy, it is important to indicate that patients who are chronic alco-

holics do not lose the ability to change ethanol into acetaldehyde, and that they may even do it more rapidly and efficiently than nonalcoholic patients.[34] This is true despite the fact that the alcohol-dehydrogenase activity which transforms ethanol to acetaldehyde as well as the aldehyde-oxidase activity which breaks down acetaldehyde both occur predominantly and almost exclusively in the liver[35] which is frequently diseased in alcoholic patients.

On the basis of the present and previous findings about the cardiovascular effects of acetaldehyde, its actions on the heart may be summarized as follows. In concentrations not infrequently occurring in acute alcoholism in man acetaldehyde rapidly releases myocardial stores of norepinephrine. This interpretation is based on the similarity of its actions to those of *tyramine or of directly administered nor*epinephrine and the fact that these actions can be reversed and blocked with specific beta-receptor blocking agents and are not observed in the reserpinized animal. Acetaldehyde is also known to be capable of releasing norepinephrine and epinephrine from extracardiac stores including the adrenal medulla but its cardiovascular effects are nearly as prominent even after ligation of the adrenal veins.[11,13] Although circulating catecholamines released from the adrenal medulla may augment the stimulating effect of acetaldehyde on the heart the direct cardiac action is probably more important. Since the action of acetaldehyde in these and other[1] experiments could not be restored after reserpinization by the administration of norepinephrine its *norepinephrine-releasing action differs* from that of tyramine and resembles that which follows adrenergic nerve stimulation. There is no vagolytic component to the sinus tachycardia from acetaldehyde nor is there any element of sensitization to norepinephrine. Formaldehyde does not share the positive chronotropic and inotropic actions of acetaldehyde.

In the present study we performed only acute experiments and the duration of the administration of test substances was brief (5 to 10 seconds). The actions of acetaldehyde were consistent and marked under these circumstances. The absence of significant action of ethanol and of the other substances studied except in unusually high concentrations must be interpreted in view of the brief administrations and with more prolonged administration these substances may have significant effects.

Since acetaldehyde acutely stimulates the heart, one can construe its actions to be beneficial. This stimulation occurs through the liberation of cardiac stores of norepinephrine however and it has recently been demonstrated that the myocardium is deficient in norepinephrine during congestive heart failure due to a variety of causes.[37-39] If the heart of the chronic alcoholic is at all diseased then further depletion of its stored catecholamines must be deleterious, particularly if this occurs repeatedly and for a long time. In addition to the ultimate bad effects of depletion of norepinephrine the acute stimulation during the course of release of norepinephrine may be thought of as whipping a tired horse. This is particularly the case if substances (including ethanol) with cardiac depressant actions are simultaneously present. Furthermore chronic repeated cardiac stimulation of the heart with catecholamines (as in pheochromocytoma) may directly damage the myocardium.[40]

In addition to its norepinephrine releasing action acetaldehyde is also capable of releasing serotonin.[41] Serotonin has only a weak negative chronotropic action on direct perfusion *of the sinus node*[42] *but* under certain circumstances may stimulate the heart.[43] Whether this contributes to the final effect of acetaldehyde on the heart in alcoholic patients is uncertain but the action of acetaldehyde in releasing norepinephrine seems more likely to be the important one.

One of the puzzles in alcoholic cardiomyopathy is why among patients consuming similar amounts of ethanol and eating reasonably comparable adequate diets, some develop heart disease and others do not. Undoubtedly the presence of associated problems, such as coronary atherosclerosis or viral infections may account for some of this discrepancy. We may also consider possible individual differences in response to the release of norepinephrine by acetaldehyde. Those patients with generous stores of myocardial norepineph-

rine may get profound stimulation during the acute effects of acetaldehyde whereas those with smaller stores may not. Similarly there must be individual variation in the ability to resynthesize depleted stores of norepinephrine. Those alcoholic patients with a high level of such ability may not develop the ill effects of catecholamine depletion for a long time or at all whereas those with poor ability to replace norepinephrine m y l v l q rdia h case soon

Summary

In anesthetized dogs direct perfusion of the sinus node with t l l hy le produced mark l t mul t on in ncentrations similar to those urring in human alcoholism. Ethanol and closely related compounds had only depressant effects which during these experiments were observed only with unusually high concentrations. The stimulating action of acetaldehyde presented that it was not altered by atropinization, could be reversed and blocked with propranolol and was totally absent after reserpinization, which suggests that it is due to the direct release of myocardial norepinephrine. Both the acute and chronic cardiac effects of alcoholism may be due in part to the release of myocardial norepinephrine by acetaldehyde, the principal metabolite of ethanol.

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ECG changes resulting from cerebral stimulation

III. Action of diphenylhydantoin on arrhythmias

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Although diphenylhydantoin (Dilantin) sodium has long been recognized as an efficacious anticonvulsant agent, its value in the treatment of cardiac arrhythmias has only recently been acknowledged.

The first experimental study demonstrating the effect of diphenylhydantoin upon ventricular arrhythmias in dogs was reported by Harris and Kokernot. They found that relatively large doses of the drug abolished ectopic ventricular activity induced by coronary artery occlusion.

Other investigators have shown that diphenylhydantoin inhibits supraventricular[4] and ventricular[5] arrhythmias experimentally induced by pharmacologic agents.

Since previous studies[6, 7] from our laboratories have been concerned with centrally evoked cardiac arrhythmias, we decided to explore the effects of this drug on such electrocardiographic changes.

Methods

Four adult beagle dogs weighing between 9 and 13 kilograms and 24 adult cats weighing between 2.8 and 5.0 kilograms were used in this study. The experimental procedures and apparatus have been described in an earlier publication,[7] with one exception: all cats were anesthetized with ether, a tracheotomy was performed, and polyethylene catheters were inserted into the femoral artery and vein. The anesthetic was then discontinued, all wound margins were infiltrated with procaine hydrochloride, and the animals were immobilized with gallamine triethiodide (Flaxedil) administered intravenously, 2 mg. per kilogram of body weight. A sustaining dosage of Flaxedil was infused automatically at a rate of 6 mg. per hour while artificial respiration was maintained with a Harvard pump.

Symmetrical biphasic pulses (50 c.p.s., 1 msec.) with a constant current of 0.5 to 1.0 Ma. were delivered for 30 seconds,

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every 30 minutes over a period of 6 to 7 hours to loci in the ventromedial region of the hypothalamus, and the reticular formation and central gray substance of the midbrain. The stereotaxic coordinate system used for the dog was developed by Lim, Liu and Moffitt[8] and that for the cat by Snider and Niemer. Table I lists the electrode positions.

The experimental animals were divided into two groups, each consisting of 2 dogs and 12 cats. Group I received an intravenous injection of diphenylhydantoin (10 mg. per kilogram) 1 minute prior to electrical stimulation of a cerebral locus and Group II was administered an identical dose of the drug after cessation of the stimulus.

Results

Electrical stimulation of loci in the diencephalon and mesencephalon elicited cardiac arrhythmias with latencies ranging from 4 to 20 seconds accompanied by marked elevations in systemic blood pressure. These aberrant complexes of sympathetic origin included ventricular fusion phenomena, ventricular premature contractions in either bigeminy or trigeminy and ventricular tachycardia. The sequence of appearance of these ectopic ventricular rhythms was invariably the same. This spectrum was described in an earlier paper.[7]

Diphenylhydantoin in doses of 10 mg. per kilogram administered intravenously to animals in Group I at 1 minute prior to electrical stimulation of a cerebral locus prevented the induction of cardiac arrhythmias. Fig. 1 from a dog illustrates this effect.

An identical dose of the drug given to animals in Group II abolished aberrant complexes that had been elicited previously by electrical stimulation. Figs. 2 and 3 illustrate this effect in tracings from both the dog and cat.

It should be mentioned that, after the cessation of a stimulus, abnormal complexes continued for periods up to 5 minutes or more. When an initial stimulus of 0.5 Ma. failed to prolong the induced arrhythmias for at least 2 minutes, the intensity was increased to 1 Ma., a level which always proved to be effective under these experimental conditions. The time course of the effect of diphenylhydantoin was assessed by delivering electrical stimuli to a given neural locus every 30 minutes after administration of the drug over a period of 6 to 7 hours (duration of an experiment). It was observed that the blocking effect upon the induced ectopic ventricular activity was variable, i.e., diphenylhydantoin either prevented the induction of or abolished ectopic ventricular activity for periods of 30 minutes to 7 hours. When the blocking effect was short lived, e.g., 30 minutes, a supplementary dose of 5 mg. per kilogram was usually effective in preventing the arrhythmias for the remainder of the experimental session.

Discussion

The results from these experiments show that diphenylhydantoin exerts a significant depressive influence upon ventricular arrhythmias induced by electrical stimulation of the central nervous system.

As mentioned earlier, Harris and Kokernot[3] abolished ectopic ventricular impulses resulting from acute myocardial infarction in dogs with doses of diphenylhydantoin ranging from 125 to 200 mg. per kilogram of body weight. They suggested that this drug acted directly upon the myocardium and likened its action to that of an anti-

*Dilantin, Parke, Davis & Company, Detroit, Mich.

Table I. Coordinates of electrode placements from which responses were elicited in diencephalon and mesencephalon

	Anterior to interaural line (mm.)	Lateral to midline (mm.)	Depth from interaural line (mm.)
Dog			
	20	1.5	+6
	20	2	+6
	11	2	+15
	9	2.25	+13.5
Cat			
	10	1.5	−5.5
	2	1	+1
	2	2.5	−3
	2	3	−3

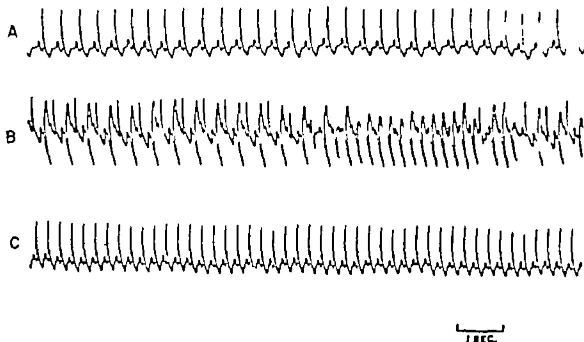


Fig 1 [illegible] B represen[illegible] during electrical stimulation of the central g[illegible] of the mesencephalon [illegible] C [illegible] recorded during stimulation of the [illegible] 1 min [illegible] after the administration of 10 [illegible] per kilogram of diphenylhydantoin (Dog No 1)

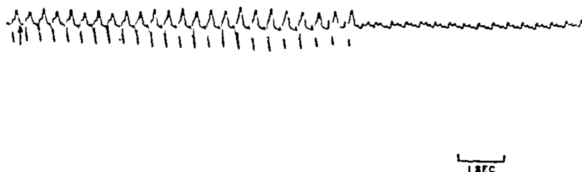


Fig 2 The arrow indicates the end of infusion of 10 mg per kilogram of diphenylhydantoin. The run of ventricular tachycardia was recorded after the offset of electrical stimulus to the ventromedial region of the hypothalamus (Cat No. 6)

convulsant agent by drawing an analogy between the area surrounding a myocardial infarction and the boundary region around cerebral post traumatic scars and lesions.

Although the precise mode of action of diphenylhydantoin has yet to be elucidated Woodbury[20] reported that this drug administered to normal rats, decreased the excitability of the brain as measured by the animal's electroshock seizure threshold (EST) He showed that diphenylhydantoin decreased the total as well as the intracellular concentrations of sodium in the brain tissue and that the increased ratio of extracellular to intracellular sodium bore a direct relationship to the EST Woodbury also demonstrated a decrease in intracellular sodium in skeletal and heart muscle but to a lesser extent than in brain tissue In view of this latter finding

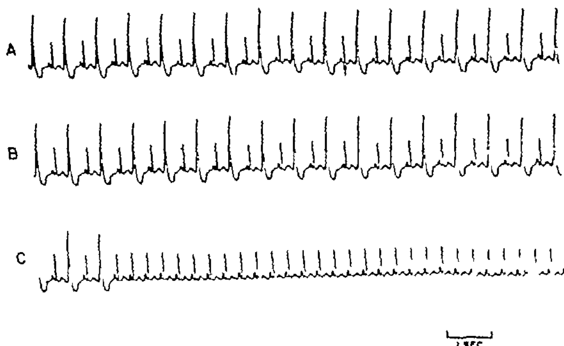


Fig. 3. A, B, and C represent a continuous tracing recorded after cessation of electrical stimulation of the mesencephalic reticular formation. Administration of 10 mg. per kilogram of diphenylhydantoin, at arrow, converted the bigeminal pattern (Dog No. 2).

it has been inferred[2] that diphenylhydantoin might decrease myocardial excitability by stimulating metabolic processes involved in the active extrusion of sodium from the cell, thereby raising the membrane threshold and suppressing ectopic activity. As Woodbury has pointed out, however, this hypothesis remains to be tested.

Since Woodbury demonstrated that the decrease in intracellular sodium was greater for brain than for cardiac tissue after diphenylhydantoin, it appears to be reasonable to suggest a central nervous system selectivity for the drug in the present series of experiments. The dosage administered, i.e., one tenth to one twentieth of that used by Harris and Kokernot, gives additional support to the hypothesis of a central rather than peripheral action.

Summary

Electrical stimulation of diencephalic and mesencephalic loci, in both dogs and cats, elicited a spectrum of ventricular arrhythmias which frequently persisted for 5 minutes or longer after the offset of the stimulus. Intravenous administration of 10 mg. per kilogram of diphenylhydantoin sodium not only abolished these ectopic ventricular rhythms but also prevented their induction by a subsequent stimulus for periods varying from 30 minutes to 7 hours. A possible central nervous system action for the drug is suggested.

We wish to express our gratitude to Mr. F. T. Grove, Mr. M. D. Banks, and Mr. J. H. F. Pervall for technical assistance.

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Case reports

Bony metaplasia in the wall of the aorta in a full term fetus

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Bony metaplasia has been reported frequently both in nonneoplastic and neoplastic tissues. The bone is often present in the walls of sclerotic calcified arteries. Mönckeberg[1] reported the first case of bony metaplasia in the walls of sclerotic calcified arteries. Bunting[2] noticed the presence of bony masses underlying atheromatous patches and adjacent to the calcified media of the aorta in a 7[illegible] year-old man; the bone contained vascular marrow with fat cells, hemopoietic cells, and megakaryocytes. Willis, in 1930 at the Alfred Hospital, Melbourne, Australia, examined a collection of sections of arteries from diabetics that showed bone formation with hemopoietic marrow in cases of medial calcification, even in young subjects. On a review of the literature we have not been able to find any case report of the occurrence of bony metaplasia in the aortic wall during intrauterine life. The present is an unusual case of aortic bony metaplasia noticed incidentally in a full term fetus.

Case report

A full-term male fetus which died during the labor of the mother was sent to the Department of Anatomy, Government Medical College, Patiala.

Gross [illegible]. When the upper portion of the ascending aorta was opened, a well-delineated oval shaped plaque, 1.2 by 0.5 cm., was seen just distal to the ductus arteriosus on its posterior wall 6 cm. away from the origin of the aorta. The endothelium overlying the plaque was of normal color. The wall of the aorta near the plaque was firm and, when cut, was of gritty nature (Fig. 1).

Microscopic [illegible]. The paraffin section prepared from the plaque and stained with hematoxylin and eosin showed trabeculae of well-differentiated bone in the upper portion of the media underlying the thin layer of intima. The bone contained fat cells, hemopoietic cells, and megakaryocytes. The paraffin section from the adjoining portion of the wall also showed trabeculae of well-differentiated bone containing hemopoietic cells and fat cells in the deeper portion of the media. No cartilage or calcified areas were seen anywhere in the wall of the aorta. The section from the wall of the aorta from the distal region showed no pathology (Figs. 2 and 3).

Discussion

Heterotopic bone marrow containing hemopoietic cells and fat cells in varying proportions is seen in the metaplastic bone. The bony metaplasias have been recorded in various tissues such as reparative tissues, scars, organizing hematomas, skeletal muscles, old caseous tuberculous lymph nodes, and nodular goiters. There

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g 1 Photo gr ph of the he rt nd the ar h of the rt show ng port on of the plaque t the right per margin of the aort



Fig 2 Photomicrograph from the plaqu showing well-differentiated bone containing fat cells nd hemopoietic cells. Hematoxylin and eosin, X70.



Fig 3 Ph tom rograph from the portion of he aort w ll adjoining the plaque showing t becul of well-differentiated bone containing hemopoetic ells Hematoxyli nd eosin X 0

are a number of reports of metaplastic bone formation in sclerotic calcified ar teries.[2] Bony metaplasia ha also been reported in the arteries of diabetics even in young subjects. In all of the cases so far reported in the liter ture bony meta plasia was second ry to some lesion but in the present case we could not find any lesion in the wall of the aorta.

Summary

A case of bony metaplasia in the wall of the aorta containing heterotopic hemopoietic tissues in a full term fetus has been reported and the relevant literature on the subject has been reviewed

M O P Khosla prepared the photomicrographs.

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Congenital dextrocardia with anterior wall myocardial infarction

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Myocardial infarction has been reported infrequently in patients with either mirror-image or isolated dextrocardia. The present report is a case of myocardial infarction occurring in a patient with congenital mirror-image dextrocardia associated with situs inversus. That condition is described in which the unequivocal electrocardiographic changes of myocardial infarction are present in the right precordial leads. An eighteen lead electrocardiogram recorded before and twenty-four lead electrocardiograms recorded during and after acute myocardial infarction are presented, as well as vectorcardiograms after infarction.

Case report

A 52-year-old Puerto Rican merchant seaman with known dextrocardia and complete situs inversus has been followed at the United States Public Health Service Hospital, Staten Island, N. Y., since October 1962. On May 17, 1963, he was admitted to another hospital after the sudden onset of sharp, persistent pain in the right side of the chest which radiated to the neck and right arm and was accompanied by nausea, vomiting, weakness, and sweating. There were no symptoms of congestive heart failure.

Physical examination revealed a well-developed, restless man in acute distress due to pain in the right side of the chest and right arm. The blood pressure was 145/95 mm. Hg with a regular pulse of 78 beats per minute. There were moist, bilateral, basilar râles in the lungs. The heart, located by percussion and auscultation to be in the right hemithorax, revealed no abnormal sounds or murmurs. The liver, palpated below the left hemidiaphragm, was not enlarged. The right testicle was lower than the left. The remainder of the physical examination was unremarkable.

The electrocardiogram recorded before the myocardial infarction (Fig. 1) shows the classic changes of uncomplicated mirror-image dextrocardia. The rightward P, QRS, and T vectors are reflected in the inverted deflections in Lead I, and the P, QRS, and T waves recorded from left to right across the right precordium are those normally seen from right to left across the left precordium. In congenital dextrocardia of the mirror-image type with situs inversus, the electrocardiogram may be read in normal fashion if the arm lead wires are reversed and the precordial leads are taken from left to right over the right precordium.

The electrocardiogram recorded with the arm lead wires reversed at the time of the acute myocardial infarction (Fig. 2) shows the following abnormalities: Q waves, S-T segment elevations, and T wave inversions in Leads I and AVL and in the right precordial leads. Serial tracings revealed changes consistent with evolving anterior wall myocardial infarction. Electrocardiographic abnormalities characteristic of infarction (Fig. 3) have persisted for 2 years and 9 months.

Laboratory studies on admission revealed a white blood cell count of 14,400 with 68 per cent

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Fig 1 Photograph of the heart and the arch of the aorta showing a portion of the plaque at the right upper margin of the aortic wall



Fig 3 Photomicrograph from the portion of the aortic wall adjoining the plaque showing trabeculae of well-differentiated bone containing hemopoietic cells Hematoxylin and eosin, ×70



Fig 2 Photomicrograph from the plaque showing well-differentiated bone containing fat cells and hemopoietic cells. Hematoxylin and eosin, ×70

are a number of reports of metaplastic bone formation in sclerotic calcified arteries. Bony metaplasia has also been reported in the arteries of diabetics, even in young subjects. In all of the cases so far reported in the literature bony metaplasia was secondary to some lesion but in the present case we could not find any lesion in the wall of the aorta.

Summary

A case of bony metaplasia in the wall of the aorta containing heterotopic hemopoietic tissues in a *full term fetus* has been reported and the relevant literature on the subject has been reviewed

Mr O P Khosla prepared the photomicrographs.

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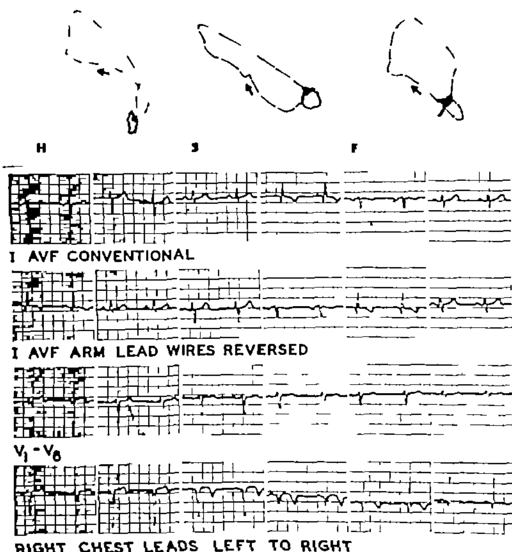


Fig. 3. March 1, 1966. Vectorcardiogram and twenty-four-lead electrocardiogram recorded 2 years and 9 months after myocardial inf rtion. The sagittal vectorcardiogram illustrated is right sagittal vectorcardiogram.

segmented neutrophils and 9 per cent band forms, an erythrocyte sedimentation rate of 13 mm. per hours, and serum glutamic oxaloacetic transaminase of 132 units. These returned to normal within the next few days. The patient was treated with bed rest, digitalis, mercurial diuretics, and anticoagulation and an uneventful hospital course ensued. He was discharged after 41 hospital days. Since discharge the patient has been seen every one to 1 months, and is currently under treatment for symptoms of angina pectoris. His heart is ell compensated on digitalis.

Discussion

Among the previously reported cases of congenital dextrocardia with myocardial infarction[-4] situs inversus was absent in only one case.[4] The published information as summarized in Table I suggests that there is little difference in the clinical course of coronary heart disease in patients with situs inversus dextrocardia as compared with those whose hearts are in the normal position. One interesting exception to this statement is the fact that in virtually all reported cases of dextrocardia including our own the pain of myocardial infarction was entirely or predominantly on the right side rather than on the left side (Table I).

Table I. Cases of mirror image dextrocardia with myocardial infarction

Case, year reported	Age at first infarction, sex	Acute mortality	Significant Q waves right lower chest	Anatomic localization of infarct	Location of pain	Hypertension	CHF	Chronic angina	SGOT
Crawford, 1938	58, M	0	0		Right anterior chest	0	+	+	—
Gerbin, 1944	43, M	0		Anteroapical	Substernal, radiating to both shoulders	0	0	—	—
Mercer, 1948	73, M	0	+	Anteroseptal	Substernal radiating to right arm	+	—	—	—
Walker, 1951	57, M	0	0	Infero-posterior	Inferior to right scapula	—	+	+	—
Fischer, 1958	49, F	0	+	Anteroseptal	Right upper abdomen, no radiation	—	+	—	—
Jacoby, 1963	53, M	0	0	Inferior	Right anterior chest, right shoulder and arm		0	—	
Kirk, 1965	67, M	+		Inferior (old) Anterolateral (recent)	Precordial	+			
Cronotha, 1965	70, F	+	0	Anterior	Right side of chest, right arm		0	+	
Present case, 1967	52, M	0	+	Anterior	Right arm, right neck, right anterior chest	+	+	+	↑

CHF = Congestive heart failure. + = Present. 0 = Absent. — = Not mentioned. ↑ = Less than.

The previous reports suggest that difficulty was encountered in only one case with regard to the diagnosis of myocardial infarction in the presence of dextrocardia. In this patient an exploratory thoracotomy was performed for possible malignancy or pericardial cyst suspected from the history of pain beneath the right scapula. At operation dextrocardia was noted with a ventricular aneurysm involving the posterior surface of the systemic ventricle. In this case the electrocardiogram demonstrated broad Q waves in Leads II, III, and AVF and in the right posterior chest leads.

None of the previously reported cases of myocardial infarction with dextrocardia[1-9] is documented by a normal eighteen lead electrocardiogram before infarction. In the case here reported the preinfarction electrocardiogram (Fig. 1) exemplifies the normal pattern of mirror image dextrocardia and the electrocardiogram taken on admission to the hospital (Fig. 2) shows the typical changes of acute anterior wall myocardial infarction as previously described. Electrocardiograms in this case (Figs. 2 and 3) and in 4 previously reported cases[4-7] reveal unequivocal QRS, S-T, and T changes of myocardial infarction in the right precordial lead.

In one previous case of dextrocardia with myocardial infarction, vectorcardiograms were recorded; these revealed an inferior infarction. In the patient whose case is here reported, a vectorcardiogram (cube reference frame) was obtained at the time of the latest electrocardiogram (Fig. 3). In the horizontal plane the loop is clockwise and oriented to the right and posteriorly with obliteration of the normal anterior forces and a wide QRS-T angle. The right sagittal loop has a clockwise superior and posterior orientation with no anterior forces; the wide QRS-T angle and the symmetrical inscription of the T loop are clearly seen. In the frontal plane there is a clockwise loop oriented to the right and superiorly with a small initial leftward inscription. These abnormalities are a mirror image of those recorded vec

torcardiographically in anterior wall infarction in the normally placed heart.

Summary

A case of anterior wall myocardial infarction in a patient with congenital dextrocardia with situs inversus is presented. The clinical electrocardiographic and vectorcardiographic findings are discussed with reference to the pertinent literature.

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Sickle cell trait complicated by sickle cell thrombi after open heart surgery

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Sickle cell trait rarely produces symptoms under normal circumstances; however, sickle cell thrombi can occur under conditions of low oxygen tension.[1,2] Sickle cell trait is therefore a potentially serious problem in patients with cardiopulmonary disease.

The purpose of this report is to emphasize the importance of sickle cell trait in patients requiring cardiopulmonary bypass.

Case report

A 58-year-old Negro grocer presented himself for diagnosis and treatment of progressive congestive heart failure. He was discovered to have had syphilis in 1945 and was treated for this disease in 1945 and again in 1953. In 1959, 1962, and 1964 he suffered myocardial infarctions. After the infarction in 1962, his heart function deteriorated relentlessly. At the time of admission, he was completely incapacitated by congestive heart failure in spite of bed rest and treatment with diuretics.

Past medical history revealed no other serious illness or operations. He was never known to be anemic nor was there any known familial history that suggested anemia.

Physical examination revealed a 58-year-old Negro man who was emaciated, chronically ill, and apprehensive. His blood pressure was 160/30 mm. Hg, respiration 24 per minute, temperature 97.6°F, and pulse 80 per minute and irregular. There were mild arteriosclerotic changes of the ocular fundi. The heart was grossly dilated and there was a decrescendo diastolic murmur of aortic insufficiency and signs of congestive heart failure (enlarged liver, ankle edema, and third heart sound gallop rhythm).

The electrocardiogram showed evidence of the old infarctions. The heart was enlarged radiographically and the enlarged, calcified, ascending and transverse aorta was seen. There was x-ray evidence of lymphatic and venous congestion of the lungs, with fluid in the costophrenic angles. The hemoglobin was 12.8 Gm. per cent, hematocrit 40.5 volumes per cent, WBC 8,000 per cubic millimeter with a normal differential count. Urinary specific gravity was never over 1.011 on four separate sporadic determinations. The urine pH was 5.5, protein 150 mg. per cent, glucose none, and there were 10-20 RBC, 28 WBC, 9-10 hyaline casts, and 10-20 finely granular casts. The blood urea nitrogen was 32 mg. per cent, prothrombin time 78 per cent; and serologic tests for syphilis were reactive.

Hospital course. The patient was digitalized on admission. Subsequently, cardiac catheterization revealed no evidence of intracardiac shunt. The pulmonary arterial pressure was 85/40 mm. Hg, the left ventricular pressure was 175/25 mm. Hg, and the central aortic pressure was 175/50 mm. Hg

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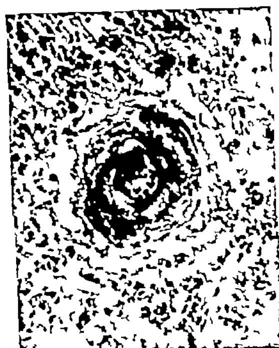


Fig. 1. Small cerebral arteriole containing organized thrombus with sickle cells.

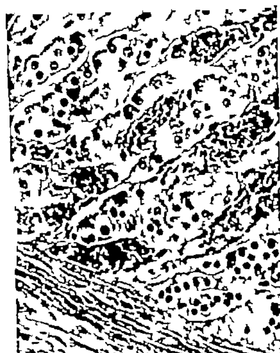


Fig. 3. Section of adrenal cortex showing capillaries congested with sickle cells.



Fig. 2. Splenic sinusoid congested with sickle cells.

Marked aortic insufficiency was evident cineangiographically.

Because it was thought that aortic valve replacement would improve his condition, his incompetent aortic valve was replaced with a Starr-Edwards prosthetic valve while circulation was maintained by extracorporeal pump and oxygenator. A disposable "bubble-type" oxygenator was used which was primed with 5 per cent dextrose and water. The total pump time was 41 minutes, and the patient's circulation was dependent on artificial perfusion for 30 minutes. The coronary arteries were cannulated and perfused during the dependent time. He received four units of type-specific blood during the operation. The volume of flow during the period of extracorporeal circulation was 80 c.c. per kilogram per minute.

Postoperatively, he never fully regained consciousness. Although awake he was confused and disoriented. Over the next 23 days, he showed progressive cerebral deterioration as indicated by Cheyne-Stokes respiration, dilation of the pupils, episodes of coma, cardiac arrhythmia requiring external cardiac massage and external countershock, partial paralysis of the upper and lower extremities, bilateral Babinski reflexes, and lack of voluntary actions. The impression at the time of his death was pulmonary abscesses with disseminated septic emboli, including cerebral abscesses.

Necropsy revealed, in addition to syphilitic heart disease and moderate to severe atherosclerosis, multiple pulmonary, renal, coronary, and brain infarctions due to sickle cell thrombi. Sickling of

the red cells was noted ... rtuall ... ll org ... m histologic examination. The spleen w ... nor ... ul size ... nd contained sickled red cell ... engorged rterioles nd i ... the sinusoids, but no ... fa ... t were present. Only the pulmonary inf rc t w ... sec ndar ly bacterially ... ont minated ... nd they ... lone showed bscess formation ... M ... scopic ll ... the infar t surrounded small rterioles ... h h ... on ... ni ... kle cell thrombi.

Retrospectl ely the ... d ... ed ... knowledge of anemia or sickle ... ell rises ... the patie t ... any of the patient ... f mil ... Hemoglobin ... lectro phoretic ... tudy of the pa ient ... hildren demon trated that hemoglol ... A nd S ... present in one of the sibl g ... here ... the ... her h d ... nl normal hemoglobin A

Comment

It is well kn own th t event which are associated with l w oxygen tension c in cause sickl ng c f erythrocytes that possess the sickle ll trait Furthermore it ha been sh wn th t decreasing pla m i pH increases kl ng Such processes as extra corporeal irculation anesthesia atelc ta sis and drug induced respiratory depression could all be easily incriminated as triggering sickle cell thrombi either by alveolar or oxygenator hypoventilation or metabolic acidosis. Any of these might occur during or after the perfusion Harri has described successful surgical repair of congenital heart disease with coexistent sickle cell disease in 2 patients His method of transfusion prior to oper ition to the point of replacing electrophoretically de tectable SS hemoglobin and then priming the extracorporeal oxygenator with whole blood might avoid the possibility of thrombi occurring during the periods of low oxygen tension or decreased pH which accompany such surgical procedures. In patients with sickle cell trait it might be judicial to prime the pump oxygenator with whole blood instead of dextrose and water in an attempt to decrease the per centage of erythrocytes that would sickle under conditions of low oxygen tension or reduced pH that may be associated with open heart surgery Furthermore it would appear to be important to be alert t the presence c f sickle cell trait in any patient requiring open he irt surgery

Summary and conclusions

Sickle cell tr iit under normal conditions produces few symptoms but i a potential thre it to the succe ful management of patients und rgoing procedures which ex pose them to l w oxygen ten ions or a reduction in pla ma pH A patient with undiagnosed sickle cell trait with severe a rtic regurgit ition was surgically tre ited b y replacement of the aortic v ilve while circulation was maint iined b y extracor poreal oxygenation Subsequently he de veloped signs of damage to the central nervous system in l ultimately died At postmort m examination multiple sickle cell thromb i were found with infarctions c f brain heart and kidney The spleen w s c f normal size

It i postulated that either during per fusion or postoper itively a low oxygen tension or reduced plasma pH resulted in the intravascular sickling This prol lem might have been exaggerated b y priming the oxygenator with dextrose solution since th use of homologous blood would have diluted the cells containing sickle hemoglobin

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Clinical pathologic conference

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Kurt Amplatz M.D
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DR. DAVACHI This male child was born after an uncomplicated pregnancy Although no murmur was present at birth a systolic murmur was evident at 2 weeks of age The infant remained asymptomatic until 3 months of age when examination revealed a stiff neck an enlarged liver and dyspnea. Subdural effusion was diagnosed and treated by repeated subdural taps. Until the age of 7 months the infant appeared intermittently cyanotic and had several episodes of pneumonia and was hospitalized. During one of these admissions he was digitalized because of evidence of congestive cardiac failure. At the age of 10 months he was admitted to the University of Minnesota Hospitals for evaluation of the cardiac murmur

On admission the physical examination revealed a small ill appearing infant who was questionably cyanotic. A left precordial bulge and cardiomegaly were evident A Grade II IV systolic murmur was best heard at the fourth and fifth left intercostal spaces. In addition a Grade II short middiastolic murmur was heard at the fourth left intercostal space. The second sound was split and the pulmonic component was louder than normal. No hepatosplenomegaly was evident. Radial and femoral pulses were good

An electrocardiogram revealed left axis deviation right atrial hypertrophy and biventricular hypertrophy Thoracic roentgenograms showed moderate cardiomegaly and increased pulmonary arterial vascularity The urinalysis gave normal results, and the concentration of hemoglobin was 15 2 Gm. per 100 ml of blood

Cardiac catheterization was performed during this admission and revealed an increase in oxygen saturation at both the atrial and the ventricular levels, with pulmonary hypertension. The infant was treated with antibiotics and digitoxin with improvement in his clinical status and was discharged from the hospital

At the age of seven the patient was readmitted for evaluation for cardiac surgery He presented as a small acyanotic 7 year old boy Cardiomegaly was present. In the third and fourth left intercostal spaces, a systolic thrill accompanied a Grade III/IV pansystolic murmu The pulmonic com

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ponent of the second cardiac sound was accentuated. There was no evidence of cardiac failure.

Dr. Moller, would you please elaborate on the electrocardiogram and vectorcardiogram.

DR. MOLLER. In studies of the patient at the age of seven years (Fig. 1) the scalar electrocardiogram reveals several features commonly observed in patients with endocardial cushion defect (persistent common atrioventricular canal). The first is the presence of left axis deviation. The P waves in Leads II and V_1 are abnormally tall with a broad base, which suggests right atrial enlargement. In addition, the P-R interval is at the upper limits of normal (0.20 seconds.) I would interpret the precordial lead to indicate right ventricular hypertrophy because of the predominant R wave in Lead V_4R, the positive T wave in V_1, and the very deep S wave in Lead V_6. These findings are distinctly abnormal for a 7-year-old child. On the other hand, I see no evidence to suggest left ventricular hypertrophy. In addition, there is a suggestion of a terminal delay of ventricular activation, which suggests incomplete right bundle branch block.

The vectorcardiogram reveals a counterclockwise inscription of the QRS loop in the frontal plane, which is observed in individuals with left axis deviation. The important feature is the clockwise inscription of the QRS loop in the left sagittal plane (this indicates right ventricular hypertrophy). This is substantiated in the horizontal projection by a clockwise inscription of the vector loop with significant rightward and posterior forces. There is a delay in the terminal electrical forces.

I would interpret both the scalar and vector electrocardiogram to indicate an endocardial cushion type of defect with marked right ventricular hypertrophy.

DR. DAVACHI. Dr. Amplatz, would you please read the roentgenograms?

DR. AMPLATZ. The thoracic roentgenograms at 10 months of age (Fig. 2, *a* and *b*) and at 7 years of age (Fig. 2, *c* and *d*) show essentially the same observation. There is cardiomegaly with a prominent pulmonary

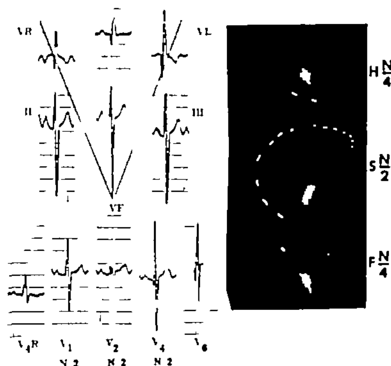


Fig. 1. Electrocardiogram and vectorcardiogram at the age of seven years.

segment and increased arterial vasculature of the lungs. This would indicate an intracardiac shunt. The peripheries of the lungs are clear which suggests pulmonary hypertension. The absence of significant left atrial enlargement might suggest the presence of an atrial septal defect as well. There is also prominence of the anterior thoracic wall particularly evident when the patient was 7 years old.

DR. DAVACHI: A second cardiac catheterization (Table I) was performed when the patient was 7 years old. An aortogram was normal. Dr. Moller, would you discuss the catheterization data?

DR. MOLLER: In this boy, cardiac catheterizations were carried out at the ages of 1 and 7 years. The first study revealed several abnormalities. The right ventricular pressure was elevated and nearly identical to that obtained in the left ventricle. The pulmonary arterial pressure was not meas-

Table I. Summary of cardiac catheterization data when the patient was 7 years old

Site	*Pressure (mm. Hg)*	*Oxygen saturation (per cent)*
Superior vena cava	—	58
Right atrium (mid)	M = 15	70
Right atrium (posterior)	—	76
Inferior vena cava	—	80
Right ventricle (high)	102/0-20	91
Right pulmonary artery	90/56, M = 66	87
Right pulmonary arterial wedge	M = 16	No flow
Left ventricle	113/0-18	96
Aorta	116/80, M = 90	—
Right brachial artery	128/86, M = 94	94

Systemic flow 2.9 L. per minute; pulmonary flow 8.10 L. per minute.
Systemic resistance, 37 units; pulmonary vascular resistance, 6.3 units.



Fig. 2. Roentgenograms of the thorax at the age of ten months (a and b) and the age of seven years (c and d).

ured, so we do not know whether the elevation of right ventricular pressure represents pulmonary hypertension or pulmonary stenosis. The pressures recorded in the atria were elevated, indicating some degree of cardiac failure. The fact that the pressures are equal would suggest an interatrial communication.

The data for oxygen saturation revealed a significant increase in oxygen content between the venae cavae and the right atrium, indicating a left-to-right shunt at the atrial level. There was a further increase in oxygen saturation between the right atrium and right ventricle, which suggested an associated ventricular septal defect. Such a finding, however, is frequently observed in isolated atrial septal defects because of streaming and better mixing in the ventricular chamber.

The second study revealed findings similar to those obtained at the time of the first cardiac catheterization. Again, a left-to-right shunt is demonstrated at the atrial level. The value of 91 per cent in the high right ventricle indicates a shunt at this level also, with the site of sampling by the catheter probably being near the defect. The saturation of 94 per cent obtained in the right brachial artery is borderline and could either be normal or suggest a minimal right-to-left shunt.

In this study the catheter entered the pulmonary artery, and pulmonary hypertension was demonstrated. In view of the size of the shunt, the pulmonary arterial resistance is probably only minimally elevated.

Considering that the electrocardiogram reveals a pattern of an endocardial cushion defect and the catheterization data indicate both atrial and ventricular septal defects, my impression would be ostium primum atrial septal defect (persistent common atrioventricular canal) with a ventricular component. In general, I feel it is uncommon with isolated ostium primum atrial septal defect to have this degree of pulmonary hypertension, so that the ventricular component may be significant.

The diagnosis could be considerably strengthened by angiocardiography. Certainly a left ventriculogram would reveal the degree of competence of the mitral valve and might reveal a "goose neck" deformity of the left ventricular outflow tract if this is, in fact, an endocardial cushion defect. Right ventriculography might also have been useful and was probably indicated because of the pulmonary hypertension.

DR. DAVACHI: Dr. Chesler, would you please give us the differential diagnosis?

DR. CHESLER: This patient exhibited signs of cardiac disease at an early age. A systolic murmur was detected at 2 months of age, and subsequently he had several episodes of pneumonia and congestive cardiac failure. This history is fairly typical in infants with a large left-to-right shunt at ventricular or aorticopulmonary level. The systolic murmur heard in the fourth left intercostal space and the apical middiastolic murmur would favor the diagnosis of a ventricular septal defect. Thoracic roentgenograms confirmed the presence of left ventricular hypertrophy and pulmonary plethora. Total anomalous pulmonary venous connection, persistent truncus arteriosus, and complete transposition of the great vessels are also associated with pulmonary plethora, but these patients are usually cyanotic, and therefore such conditions are unlikely possibilities in this case.

The electrocardiogram showed left axis deviation, prolongation of the P-R interval, incomplete right bundle branch block, and biventricular hypertrophy, which in conjunction with the clinical and radiological features are highly suggestive of an endocardial cushion defect. The cardiac catheterization findings provided evidence compatible with this diagnosis (i.e., shunts at atrial and ventricular levels with severe pulmonary hypertension). A left ventricular angiocardiogram would have been of assistance in this respect but is, unfortunately, not available. An aortogram, however, excluded the presence of a patent ductus arteriosus.

The possibility exists that the increase in oxygen saturation at atrial level is not the result of an atrial septal defect but of tricuspid incompetence in association with a ventricular septal defect. This could be functional and related to the severe pulmonary hypertension. Alternatively, the tricuspid incompetence may be related to a cleft tricuspid valve associated with a ventricular septal defect. Left axis deviation

may occasionally be associated with a ventricular septal defect but rarely with a prolonged P R interval and incomplete right bundle branch block in addition[3] unless the ventricular septal defect is a component of an endocardial cushion defect. The same argument would apply for coexistent atrial and ventricular septal defects which are not part of the endocardial cushion type of malformation.

The remaining possibility is the condition of left ventricular right atrial communication. This may be associated with a shunt at atrial level and a murmur like that of a ventricular septal defect. The electrocardiogram occasionally may show left axis deviation incomplete right bundle branch block, and a prolonged P R interval. Other clinical features such as fixed splitting of the second sound and a tricuspid mid diastolic murmur were however absent in this case.

In summary therefore I would favor the diagnosis of endocardial cushion defect with shunts at atrial and ventricular levels.

DR. DAVACHI The patient was operated

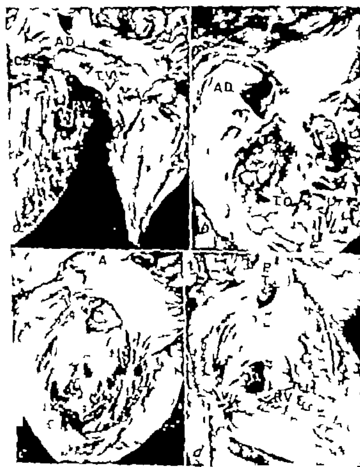


Fig 3 Right atrium, tricuspid valve (*T V*), and right ventricle (*R. V*). After removal of the repair of the atrial septal defect the defect (*A D*) is seen at the fossa ovalis. The right ventricular chamber (*R. V*) is small, and the wall of the right ventricle is thick. The ostium of the coronary sinus (*C. S*) lies near the posterior extent of the septal leaflet of the tricuspid valve. *b* Interior of right atrium from above. Defect (*A D*) of the atrial septum at fossa ovalis. The tricuspid orifice (*T O*) is small. The septal leaflet of the tricuspid valve had been incised and then sutured (arrow) near its basal attachment. *c* Left ventricle (*L V*) and aorta (*A*). The cavity is enlarged. The patch used to close the defect in the ventricular septum (*D*) remains in place. *d* Right ventricle (*R. V*) and pulmonary trunk (*P T*). The patch used to close the defect in the ventricular septum has been removed. The defect (*D*) lies posteroinferior to the crista supraventricularis. The chamber of the right ventricle is small, and its wall is thick.

upon with the aid of cardiopulmonary by pass. The left ventricle was considerably enlarged in contrast to the right ventricle which was hypoplastic

Two septal defects were found one atrial and one ventricular. The former measured 2 cm in diameter and l in the region of the fossa ovalis. The ventricular septal defect also measured about 2 cm in diameter and was considered to occupy the position of the membranous part of the ventricular septum. The mitral and tricuspid valves were normal. A Teflon patch was used for closure of the ventricular septal defect. The atrial septal defect was closed directly with interrupted silk stitches

On the first postoperative day the blood pressure was difficult to obtain and the patient developed cyanosis. Despite resuscitative measures cardiac arrest occurred and the patient died on the day of operation

DR KORNS At necropsy the principal abnormalities were confined to the cardiovascular system and lungs.

The great vessels were normally related. The pulmonary trunk was dilated the external diameters of the pulmonary trunk and aorta were 3 0 cm and 2 0 cm respectively. The venous connections with the atria were normal

The right atrium was normally formed as were the components of the tricuspid valve. The maximal dimension of the tricuspid orifice was 9 mm. The right ventricle was hypoplastic (Fig 3,*a*) with underdevelopment of the inflow portion. The septal limb of the crista supraventricularis and the outflow portion of the right ventricle were hypertrophied. The infundibulum was dilated

There were 2 intracardiac defects both of which had been closed surgically. The first was a defect in the atrial septum at the fossa ovalis. In the specimen this defect measured 1 0 cm in greatest dimension (Fig 3,*b*)

The second intracardiac defect was in the ventricular septum. This defect had been closed by being approached through the right atrium and incising the medial leaflet of the tricuspid valve at its basal attachment. The ventricular septal defect measured 2 0 cm in greatest dimension. As viewed from the left ventricle the defect lay below the posterior half of the right aortic cusp and most of the posterior aortic cusp (Fig 3,*c*). As viewed from the right ventricle (Fig 3,*d*) the defect lay posteroinferior to the crista supraventricularis and its anterior extent did not encroach upon the septal limb of the crista. The defect was located beneath the septal leaflet of the tricuspid valve and the ring of the tricuspid valve formed in part the superior border of the defect. The posterior border of the defect was 0 5 cm from the ostium of the coronary sinus and was formed in part by the conjoined anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve. No clefts were present in the valves.

Grossly the lungs showed patchy areas of emphysema and hemorrhage. There was considerable collapse in the lower lobe of the left lung. Histologically the large muscular arteries showed a moderate degree of nonspecific fibrous thickening of the intima and many exhibited elastosis of the media. The majority of the small muscular arteries and arterioles showed medial hypertrophy although a few were dilated and the media was attenuated. Rarely some of the small muscular arteries contained a plexiform lesion

DR DAVACHI Dr Edwards, would you please give a closing summary?

DR. EDWARDS It is apparent from Dr Korns description that there was an atrial and a ventricular septal defect and that these were not continuous. Therefore in spite of the clinical evidence for persistent common atrioventricular canal (endocardial cushion defect) this complex malformation was not present. The electrocardiographic pattern present in this case while considered a characteristic of persistent common atrioventricular canal has been observed in certain instances of isolated ventricular septal defect.[2] Under these circumstances, the isolated ventricular septal defect occupies a position of the ventricular septal component of persistent common atrioventricular canal.

In the case presented the ventricular septal defect exhibited certain features of the so-called A V commune type of ventricular septal defect but not all of them. The long axis of the defect was parallel to the right ventricular infundibulum while the A V commune type of ventricular septal

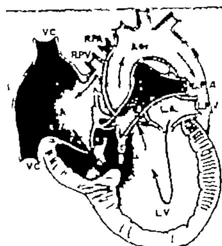


Fig. 4. Diagram of central circulation in ventricular septal defect and hypoplastic right ventricle.

defect tends to run at right angles to the septal limb of the crista supraventricularis, cutting into this structure.

Similarity between the defect of the case presented and the ventricular component of persistent common atrioventricular canal included (1) extension of the defect to the tricuspid ring and (2) continuity of mitral and tricuspid tissue.

A point of paramount interest in the case presented was the presence of a hypoplastic right ventricle (Fig. 4). This condition poses a considerable problem after the ventricular septal defect is closed. When the ventricular septal defect is open it is envisioned that during ventricular diastole, blood may flow from the right ventricle into the left. During systole, some of the accumulated blood in the left ventricle could flow through the ventricular septal defect as a left-to-right shunt. If our reasoning regarding the flow characteristics during ventricular diastole is correct, blood delivered to the aorta should not be completely saturated. The data of both cardiac catheterizations suggest the presence of a right-to-left shunt. The magnitude of this was in all probability masked by the fact that a large volume of fully oxygenated blood was returned to the left ventricle on the basis of the left-to-right shunt.

When the ventricular septal defect was closed the hypoplastic right ventricle would no longer have an escape channel during diastole and right-sided inflow obstruction could then appear.

We are not given concrete evidence for such an occurrence. Measurement of systemic venous or right atrial pressures would have been of interest to establish facts that concern the question of postoperative inflow obstruction. The low systemic blood pressure and cyanosis which were observed postoperatively may have been manifestations of such an occurrence, however.

In closing, I wish to make the point that in the patient with a ventricular septal defect associated with hypoplasia of the right ventricle, the latter may go undetected. When, however, the defect is closed, hypoplasia of the right ventricle may then assume functional importance.

Diagnosis: Atrial and ventricular septal defects with hypoplasia of right ventricle.

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The components of the Korotkoff sounds

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The series of arterial (Korotkoff) sounds that are heard [illegible] a cuff on the arm is deflated offers significant cardiovascular information in addition to the data on the blood pressure level. This additional information is contained in the intensities, durations, and patterns of the components of the arterial sounds. The present study defines these components, their mechanisms of production, and their clinical significance.

Method

A blood pressure cuff on the upper arm was inflated to a level higher than systolic arterial pressure and permitted to deflate at about 2 mm. Hg per second. The arterial sounds were auscultated and recorded.

A microphone in the antecubital fossa transduced the arterial sound to a 2 channel recording machine on which an electrocardiogram was recorded simultaneously as a reference tracing.

The present analysis is based on experience gained in the course of approximately 5,000 recordings on more than 1,[illegible]00 patients and normal individuals.[1]

Components

The arterial sounds that are heard over the arterial segment distal to the cuff have been shown to be generated during the systolic upstroke of the arterial pressure wave. Auscultation usually permits the identification of tapping and rumbling sounds. The recordings illustrate the following discrete components: opening tap, breakers, rumble, and closing bruit (Fig. 1). Silences were also recorded.

Opening tap. The opening tap, a high intensity report of brief duration, usually inaugurates the arterial sounds (Figs. 1 and 2). As the pressure wave in the artery under the cuff rises to a value that is sufficient to overcome the collapsing force of the sphygmomanometer cuff, a bolus of blood penetrates into the distal arterial segment which produces the opening tap. Near the systolic cuff pressure, where the slope of the arterial pressure wave is minimal, the amplitude of the tap is small. The amplitude of the tap increases as the cuff pressure falls to pressure levels at which the slope is steeper (Fig. 2, beats 10 through 20). As the cuff pressure approaches the diastolic value and the slope of the pressure wave decreases, the amplitude of the tap again becomes small (Fig. 2, beats 23 through 27).

As the cuff pressure falls, the difference between the pressure in the proximal and distal arterial segments at the instant of

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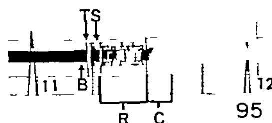


Fig. 1. Arterial sound components. This is an enlargement of beat 11 from Fig. 2. An R wave peak of the electrocardiogram is seen at the left. *B* is the breaker. *T* is the opening tap. *S* is the silence. *R* is the rumble. *C* is the closing bruit. This sound was recorded at a cuff pressure of 95 mm. Hg. See the text for full discussion.

vascular opening is reduced. This results because the pressure in the upstream segment of the artery equals the cuff pressure level at the instant of arterial wall opening, whereas the pressure in the peripheral segment of the artery rises more gradually.[3] This reduction in the pressure difference across the cuff is associated with a diminution in the intensity of the tap. Near the diastolic pressure level the pressure difference becomes small and the sounds tend to be muffled (Fig. 2, beats 25 to 27).

The steep slopes of the arterial pressure upstrokes in aortic regurgitation, in ductus arteriosus, and in generalized arteriosclerosis generate very loud opening taps. In hypertension the tapping sounds tend to be relatively faint, apparently because the low conductance (flow rate/perfusion pressure) of the peripheral vascular bed

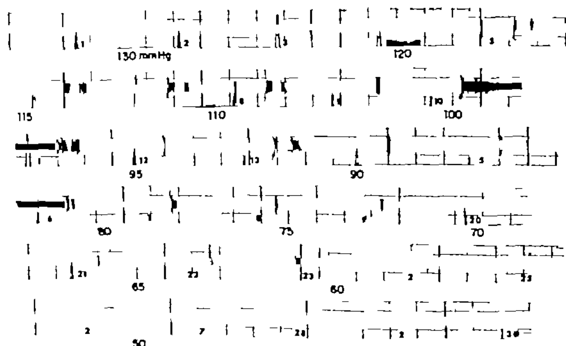


Fig. 2. Arterial sound sequence. A continuous record has been cut into 6 strips which are shown from above downward. This record was obtained on a 29-year-old man with aortic regurgitation. The beats are numbered adjacent to each R wave of the electrocardiogram or near the vertical marks placed at the peak of each R wave. Pressure levels during deflation of the cuff are given. Beat 2 shows the arterial sound at the systolic level; this consists of an opening tap. Beat 3 shows doubling of the arterial sounds observed when the arterial pressure upstroke is notched. Beat 10 shows a rumble of great intensity and duration. Beat 11 illustrates the silence located between the opening tap and the rumble as well as the closing bruit. Beat 13 shows the breaker component preceding the opening tap. Beat 27 shows a low intensity opening tap. This is the last arterial sound of the series, which designates the diastolic blood pressure level.

results in a high pressure in the arteries beyond the cuff.[3]

The opening taps are faint when the cardiac output and/or the slopes of the arterial pressure upstroke are reduced. Such faint sounds are elicited in shock, in stenosis of the mitral or aortic valves, and in congestive failure.

When the vibrational energy of the opening tap is great, the resonances generated by the acoustic impulse persist for relatively long intervals. Thus, the amplitude of the tap determines its apparent duration. By attenuating the lower frequencies of the tap, the apparent duration may be diminished. This was done by using a high band pass filter in the recording system to markedly attenuate frequencies less than 200 cycles per second.

Two sets of opening taps have been found in some patients with increased stroke volumes, especially in aortic regurgitation. Such doubling of the sounds is seen clearly (Fig. 2, beats 3 through 6). This phenomenon is usually observed near the systolic level and may be perceived by the well trained finger as an anacrotic notch or a pulsus bisferiens.

Breakers. Breakers are brief episodes of low-energy noise production which are sometimes recorded immediately preceding the opening tap at a steep portion of the arterial upstroke (Figs. 1 and 2, beats 9 through 20). These noises usually cannot be heard because they are masked by the much louder opening tap sound which follows almost at once. Breakers can be recorded consistently (10 to 30 msec.) before the onset of the tap in association with the steep arterial upstroke of aortic regurgitation or generalized arteriosclerosis.

The breakers appear to represent a portion of the energy of the pressure wave upstroke which is transmitted at velocities greater than those of the main portion of the wave. The faster moving components of each wave arrive at the cuff slightly ahead of the main portion of the upstroke. This phenomenon is similar to that observed as the crest of a wave in the sea produces breakers by falling ahead of the foot of the main portion of the wave.[6] The front running portion of the wave appears to have energy barely sufficient to extrude a small volume of fluid at high velocities through the nearly collapsed vessel before the main portion of the wave arrives to produce the much louder opening tap.

Rumble. The rumble, a low pitched rattling noise (Fig. 2, beats 8 through 15) is generated in the course of flow through a partially collapsed artery. An enhanced rate of runoff of blood out of the peripheral arteries increases the stream velocity and lowers the intra-arterial pressure locally in accord with the law of conservation of energy. As the distending pressure in the arterial segment under the cuff falls to the cuff pressure level, the vessel wall collapses, a discrete acoustic impulse is generated, and flow stops. The total energy of the stream then becomes manifest as a distending pressure which reopens the vessel as the stream accelerates, and this causes the pressure to fall again. The resulting recurrent cycle of closing and opening of the arterial segment under the cuff generates a series of discrete acoustic impulses. This murmurlike sound indicates that flow through the arterial segment under the cuff may be intermittent during the rumble phase. The resonances generated by each closure give the impression that the rumble is a continuous sound. An inspection of pressure tracings, in the segment of the artery downstream to the cuff, shows a pattern of discrete impulses. Recordings at the segment of the artery distal to the cuff show pressure oscillations which are related to the recurrent vascular closure.[3]

The intensity of the rumble varies with the instantaneous pressure difference from the proximal to the distal arterial segments. The intensity is thus affected by the state of vasodilatation (conductance) of the vascular bed of the arm. When the blood runs off rapidly out of the distal arterial segment into the widely opened capillary bed, the rumble is loud.

The duration of the rumble also varies with the peripheral vascular conductance. When conductance is maximal, as occurs in hypermetabolic states or after exercise of the muscles of the forearm, the rumble may continue for the entire duration of the pressure wave at the cuff pressure level.[7]

In conditions of diminished peripheral

vascular conductance, the opening tap and the rumble may be so faint and of such short duration that they become inaudible. Such faint sounds are usually associated with a subnormal cardiac output, as in severe aortic stenosis, mitral valvular disease, debility shock, or anesthesia. The estimation of the blood pressure in these circumstances may become indeterminate The maneuver of closing and opening the fist 10 times, which ncreases the vascular conductance of the arm can restore the intensities and durations of the sounds to levels at which the arterial pressure can be estimated with greater security

Closing bruit A closing bruit is sometimes heard at the end of the rumble especially when the arterial downstroke is steep. This bruit appears to be generated as the descending phase of the arterial pressure wave falls to a level at which the arterial segment under the cuff collapses. The closing bruit occurs especially in aortic regurgitation (Fig 1) ductus arteriosus, or arteriosclerosis.

If the rate of runoff through the peripheral tissues is high and the pressure in the arterial segment distal to the cuff is low the pressure drop will generate the high pitched blowing sound characteristic of flow through nearly closed vessels. The rumble may end with a tapping sound at the instant the central arterial pressure falls below the cuff pressure.

Silence Silence is recorded galvanometrically as an interval of relative base line stability (Fig 1) The silence between the opening tap and th rumble usually cannot be distinguished acoustically When a relatively laminar flow passes through a momentarily widely opened segment of the artery under the cuff silent intervals may be noted between the tap and the succeeding rumble The velocity of the stream in the widely opened vessel increases with the rising arterial pressure wave until laminarity is lost and the silence ends with the onset of a rumble.

Arterial silence is also evident when no cuff is present and the laminar stream moves through the vessel with negligible energy loss. Sounds are also absent when cuff pressure exceeds intravascular pressure and the vessel is collapsed and flow is obstructed

The phases of the arterial sounds

The phases of the arterial sounds observed during indirect blood pressure measurements can be evaluated on the basis of the foregoing analysis of the components of the arterial sounds.[9] The sounds of Phase I which designate the systolic blood pressure level consist of opening taps. The relatively low intensity of these taps is due to the reduced slope of the arterial pressure near systolic levels. The murmur like sounds of Phase II each consist of a combination of a tap and a prolonged rumble. The duration and intensity of these rumbles become maximal at about 25 mm. Hg below the systolic level. Phase III is characterized by loud tapping sounds followed by a rumble of short duration. In Phase IV the arterial sounds are muffled in accord with the reduced slope of the first portion of the arterial upstroke.

Korotkoff sounds and heart sounds

The components of the arterial sounds offer an instructive approach to the mechanisms of generation of the heart sounds and murmurs. The intensity of the heart sound components varies with the rate of change of the pressure drop across a heart valve at the instant of closure and sometimes, at opening [11] A small rate of pressure change, as occurs in aortic valvular stenosis during valve closure, produces a relatively faint tap while the larger pressure drop of pulmonary arterial hypertension produces a booming sound The arterial rumble bears strong acoustic resemblance to the heart murmurs. In both instances, the bruits are generated by nonlaminar flow which sets adjacent specific tissues into vibration The *durations* of the murmurs define the intervals when a significant pressure gradient is present at a constricted or stenotic segment.[11] The absence of sound indicates that flow is either laminar or obstructed Since the factors which affect the generation of the Korotkoff sounds can be controlled with ease the hydroacoustic model presented here may serve to clarify some of the mechanisms of generation of heart sounds and murmurs.

Summary

The arterial sounds include the following components (1) an opening tap generated

as the rising intra-arterial pressure overcomes the obstructive force of the compression produced by the cuff (2) a rumble generated by flow through the partially opened vibrating arterial wall (3) a closing bruit produced during the arterial downstroke as intra arterial pressure falls below the cuff pressure and (4) breakers which occur prior to the opening tap when the arterial upstroke is steep (5) Silences represent either laminar flow through a fully opened vessel or absence of flow

Similarities between the Korotkoff sounds and the heart sounds and murmurs are indicated

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Propranolol* as an antiarrhythmic agent

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This review summarizes current information concerning the use of beta adrenergic receptor blockade and in particular propranolol in the treatment of patients with cardiac arrhythmias. Propranolol has been reported to be effective in rapid heart action of all types. However review of the available literature and personal observations, have clarified the limitations and expectations.

There is at present a wide interest in adrenergic mechanisms. Until some current concepts are clarified the following suggestions as to the mode of action of propranolol and similar agents must be considered preliminary. Beta-adrenergic receptor blockade by reversing catecholamine effects, slows the sinoatrial rate and diminishes both atrioventricular junctional conductivity and ventricular excitability. This is the primary basis for propranolol's value in treating cardiac arrhythmias. In addition there appears to be a "quinidine-like" effect at higher dose levels. It has also been postulated that myocardial irritability may diminish when the heart rate is slowed and coronary flow thereby *increased*.

In addition to antiarrhythmic effects, propranolol reduces myocardial contractility. This action will be further discussed in Part II of this review. It is pertinent to mention here that awareness of this action is essential if the drug is to be used safely. Overdosage or therapy in a failing and nondigitalized heart, may cause serious hypotension or increased congestive failure.

Administration. At present intravenous propranolol should be administered in doses of 0.5 to 1 mg. at intervals of 2 to 3 minutes, with careful control of blood pressure, pulse and if possible central venous pressure. More rapid administration has been used but may be hazardous, particularly in patients with congestive failure or hypotension. Maximal intravenous doses generally should not exceed 0.1 mg. per kilogram, although 0.2 mg. per kilogram has been administered by some investigators. Effects on heart rate are usually apparent within 2 to 5 minutes and may last 4 to 8 hours. It is wise to have an intravenous infusion running with isoproterenol and atropine available in case of severe hypotension or marked bradycardia; propranolol effects can be reversed with these agents.

When propranolol is taken orally, dosages should be increased gradually (maximal dosages have not been established). Antiarrhythmic effects may be observed at times with only 5 mg. 4 times a day, but doses as high as 40 mg. 4 times a day may be necessary. In some patients, tolerance may develop and gradual increase in dosage may be required.

Atrial fibrillation and flutter. Digitalis is the drug of choice in most patients with

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*Use of propranolol, at this time, is approved for investigational purposes only.
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atrial fibrillation or atrial flutter and a rapid ventricular rate. When the heart rate is unresponsive to digitalis glycosides it usually, although not invariably, slows when propranolol is added. Intravenous treatment of such patients, as well as maintenance on oral therapy, has been a useful therapeutic supplement. Occasionally striking clinical improvement is noted in patients with severe rheumatic heart disease and uncontrollably rapid heart rates despite full digitalization. Efficacy of propranolol in these arrhythmias is due to decreased conductivity (and increased refractory period) at the atrioventricular junction. Ordinarily neither atrial flutter nor atrial fibrillation reverts to sinus rhythm with propranolol. The drug has not been very effective in maintaining sinus rhythm in patients with intermittent atrial fibrillation or flutter. However, in some patients sinus rhythm has been maintained when quinidine or procainamide could not be tolerated or, as in a few reports, when used in conjunction with quinidine.

Supraventricular tachycardia. Oral propranolol is of value in preventing recurrent supraventricular tachycardia whether spontaneous, induced by exercise and emotion, or associated with the Wolff-Parkinson-White syndrome. While all do not respond favorably in what has been a difficult clinical problem, a significant number of patients have now been treated for long periods with encouraging results. A limiting factor has been the development of marked bradycardia in some patients.

Intravenous administration of propranolol in the treatment of supraventricular tachycardias is effective in a relatively small percentage of patients. Occasionally gradual slowing of the ectopic focus occurs; reversion to regular sinus rhythm may ensue. In these arrhythmias, propranolol probably should be reserved for patients who are uncontrolled with standard drugs.

Sinus tachycardia. Protracted sinus tachycardia in a variety of clinical situations slows with propranolol. Patients without congestive failure but with persistent heart rates over 100 may have significant reduction of the resting rate as well as of exercise-induced increases in rate. It is intriguing to postulate that the rapid heart rate and increased cardiac output associated with the "hyperkinetic" heart may respond to beta blockade as hypertension responds to alpha-adrenergic blocking agents. While such slowing may not improve the patient's clinical condition, lessened awareness of heart beat may at times be of value. There are varying reports regarding effects on the rapid rate associated with hyperthyroidism. Further studies are required to evaluate the drug's usefulness in these conditions.

Spontaneous ectopic beats. Studies to date have been in conflict as to the efficacy of propranolol in treating patients with spontaneous, long-standing atrial and ventricular extrasystoles. In general, the drug has not appeared to be of great value although some responsive patients have been reported. In any case there is doubt as to the importance of suppressing these arrhythmias.

Ventricular tachycardia and ventricular fibrillation. In general, the experience with propranolol in patients with ventricular tachycardia unrelated to digitalis glycosides or other drug therapy has been discouraging. Although successful reversion of ventricular fibrillation has been reported, there is no adequate evidence to indicate that propranolol will be of major value in these patients. In some patients, after electrical defibrillation, maintenance therapy with propranolol may prove of value in preventing recurrences. At present, quinidine, procaine amide, and lidocaine are preferable to propranolol in treating these arrhythmias.

Induced arrhythmias. In these category are included those arrhythmias resulting from exercise, the emotions, anesthesia, and digitalis. Since in each of these situations adrenergic mechanisms and catecholamine release are involved, the use of beta adrenergic receptor blockade seems logical. In each category, there have been many reports of suppression of ventricular extrasystoles with propranolol.

Patients with rapid ectopic arrhythmias, in whom digitalis toxicity is suspected, may be treated with intravenous propranolol. In these patients, DC countershock is contraindicated, and in emergency situations, the choice of therapy is frequently a difficult one. The clinician is often faced with the problem of either treating the patient with

additional short-acting digitalis glycosides, or delaying therapy in the hope that time will resolve his dilemma. Preliminary evidence suggests that, if careful control is maintained of central venous pressure, blood pressure, and pulse, it may be possible to determine, on the basis of responsiveness to propranolol, whether or not digitalis toxicity exists. Thus, digitalis-induced tachycardias are frequently responsive, perhaps because increased sympathetic activity enhances the tendency of digitalis to produce such arrhythmias. If an inadequate dosage of digitalis has been administered to a patient with a cardiac arrhythmia, propranolol therapy may cause a rise in central venous pressure or a fall in blood pressure without affecting the heart rate. If this happens, further digitalization would be reasonable. Further study will be necessary in order to fully evaluate this hypothesis.

Side effects. The major hazards of propranolol were alluded to above. Decreased myocardial contractility may lead to hypotension and increased congestive failure. The heart rate may slow precipitously as a result of sinus slowing or increasing A-V block. Propranolol reduces ventilatory function in asthmatics, and is contraindicated in patients with chronic airway obstruction. The above effects are inherent in beta adrenergic receptor blockade. Deaths from these major side effects have occurred, and the importance of judicious, slow administration of the drug, with constant attention to the patient's clinical status, must be emphasized. No serious hematologic or biochemic abnormalities have been reported as yet. One patient with thrombocytopenic purpura has been reported. Transient serum transaminase rises have been reported, but there was no evidence to indicate that propranolol caused liver damage. Minor side effects such as nausea, diarrhea, rash, lightheadedness, and paresthesias have disappeared promptly when the drug was discontinued or dosage reduced. Recent reports indicate that propranolol may cause hypoglycemia in patients receiving insulin or oral hypoglycemics. The characteristic signs of catecholamine release (increased pulse and pulse pressure) may not occur. Monoamine oxidase (MAO) inhibitors or other psychotropic agents should be discontinued at least 2 weeks prior to institution of propranolol therapy.

Summary

While additional studies will be needed to clarify the role of propranolol and other beta-adrenergic blocking agents, they are important therapeutic supplements to the treatment of specific cardiac arrhythmias. They are hazardous if the clinician is not familiar with their physiologic effects.

In using propranolol or other antiarrhythmic agents, prompt treatment of such problems as anoxia, electrolyte and acid-base imbalance is essential.

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Annotations

Nonsynchronized direct current countershock

Th method of kl ring nchronized direct current (D C) u sh k l means of pacitor discharge w tr l ed b Low nd o-workers, in 1962 nd ha sin k ed lespread se in the treatment f rdia arrh hm The sig ific nce of synchr iz tion f h ou tershock problem iting t ial lim t on Ac ording to L w t l essential nch ze the D C sh k w th the cardiac le ork t id the ose lled lner able ph se h h rres ponds the in tial portion of the T

N merou repor ha discussed this method of nchronized D C defibrillation point ng out the safet nd ef lnes f he metho d nd the im portance of proper nchroniz tion Despit this general opinion sev re rd ac arrhythmias nclud g ventricula fibrillation ha been report d in connection with ynchronized D C defibrillation. View ads nced the literat re concerning the necessity of synchronization re ontradictory

W f rst used the one nd only D C defibrillator lable (without nchronization device) for emergencies, t control entricular tachy ardia in seriously ll patient After success l trial ent on sing the method in other cardiac rrh thmias. Forty episodes of hronic trial fibrillation were tre ted with nons nchronized D C. defibrillator after wh ch t prov the adv tages of synchroniza tion, if any every second ttempt at con ersion made synchronizing the D C shock well out ide the vulnerable period ll total of 76 nons nchro ized (272 shocks) nd 36 synchronized (117 shock) ttempts t defibrillation had been made. I addi tion 8 episodes of supr entricular (ith 12 shock), nd 35 episodes of entricular (ith 70 shocks) tachycardia were treated w thout synchroniz tion making tot l of 119 nonsynchronized D C. shock treatments and 354 shocks.

Atrial nodal and ventricula ectopic beat were frequently seen in both groups immediat ly after the cou tershock Instability of conduction time first-degree and second-degree heart blocks, depression or elev tion of the S-T segment in ersion of the T wave and U wav were equally ma ifest i both groups. In the synchronized group, 1 sudden death occurred 12 hours after successful cardiover sion and this was perhaps caused by an arrhythmia due t quinidine toxicity The only case of entricular fibrillation occurred in the nonsynchronized group. This happened three times consecutively during an ttempt at con ersion in patient with entricular tachy ardia. The patient in poor condi tion nd the rrhythmi may ha resulted from lectric shock given when the heart in an anoxic nd acidotic tat

The incidence of severe entricular arrhythmia in the non ynchronized gro p of the present series 3/354 (0 85 per cent) much the same as that reported by Low and co- orkers 3/600 (0.5 per cent) nd that by C st llanos nd co- orkers, 6/731 (0 82 per cent), both material ha ing been tre ted ith synchronized D C. shocks. Other orkers have reported ventricular fibrillation using nchronized D C. shock t equal or even higher frequency As uming that the ulnerable period is 0 010 second reported by Low and co-workers [17] nd that the length of the cardiac cycle is 0 75 second, the possibility of coinciding ith it is 5 4 per cent I the present series of trial fibrilla tion this ould ha happened on erage 14 6 times The pos ibility of noncoincidence ith the lnerable period is less than 1 in 200,000. I the groups of supra entricular nd entricular tachy rdia the cardiac cycle is shorter and therefore the possibility of coinciding with the ulnerable phase is greater I the present series, entricular fibrillation seen 3 consecutively times during attempt t conversion, but it seems t be likely that shocking in the lnerable period occurred all 3 times in this one case and never in the other 118 ases.

So far w ha noted no harmf l effect produced by the lack of synchronization of the D C. shock i th treatment of cardiac rrhythmias.

It ppears that the D C. shock produced entricular fibrillation i experimental imals more often if given during the lnerable period [24] or the relative refractory period The occurrence of ventricular fibrillation has, however also been show t be related to the energy employed. [14] I dogs the rat of entricular fibrillation decreased when the lev ls of energy were increased, and it was ncommon at level abov 75 joules.[14] This seem t support the iew of Nachlas and co-workers[14] that the danger of inducing fibrillation by lectric shock ppears t consist of too low current being sent through the heart. On the other hand, very high levels of energy do produce severe arrhythmias and morphologic hanges irrespective of the ardiac cycle.[10] It is claimed that synchronization of the

countershock does not eliminate or reduce the likelihood of inducing ventricular fibrillation.[10] In our opinion, too, the dangers of nonsynchronized D.C. defibrillation using the energy levels of 100 to 400 joules seem to have been exaggerated.[15] The absence of a synchronization device should by no means prevent the treatment of cardiac arrhythmias.

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Changing patterns in cardiac disability

The state of Queensland, situated between 10 and 29 degrees south latitude, has an area of 667,000 square miles. Of its population of over 1,600,000, 42 per cent of the people live in the state capital, Brisbane; 20 per cent live in 8 provincial cities. Light industry has hardly begun outside the metropolitan area. Forty per cent of the people live in strictly rural surroundings devoted to agricultural, pastoral, and mining industries. Fifty per cent are in the working age group 21-64 years. The bulk of the people are of European origin, live in a tropical or subtropical climate, and about half work in rural occupations.

Since 1954, an active program of cardiac rehabilitation has been carried out within the Commonwealth Rehabilitation Service of the Department of Social Services. This Service attempts to select potentially employable patients from those who have been receiving Social Service benefit (disability allowance) for longer than 3 months. Our results were analyzed over two 5-year periods. Hypertensive patients tended to select themselves out of the group; the bias of selection favored those with coronary, rheumatic, and congenital heart disease. Of the cardiac patients selected, 65 per cent were successfully rehabilitated. Twenty per cent of all cases were misdiagnosed or the patient had an iatrogenic cardiac neurosis, but 50 per cent of all patients seen had significant sociopsychological disability, e.g., low intelligence, social and educational retardation, frank personality defect. Of patients followed up 65 per cent were still working after 5 years.

For some 5 years, the National Heart Foundation of Australia has conducted a Work Assessment Center in Brisbane. The bias of selection has favored persons with coronary heart disease. Some 70 per cent of its patients have been successfully rehabilitated, which compares with figures obtained in the other centers of Australian states and overseas. Again cardiac neurosis was found to be a significant factor preventing rehabilitation.

Queensland is unusual in that all claims for workmen's compensation for heart disease through the State Government Insurance Office are heard by a tribunal, the Cardiac Board, composed of three physicians. This Board has functioned successfully for some 5 years and has dealt with more than 1,000 persons with well-documented industrial histories. Generally, in fatal cases autopsy evidence is available. Most claims are heard within 3 to 4 months of

th clinical onset of the disease mal ly coronary disease

I formation is st ll bei g nal zed but there is suggestion that phy icians hould keep mind as t whether ph l eff rt determine cardiac infarction Be tha t ma the fact emerges that ell over 90 per t f proof tal L ms are terminated nd the pat t re back t ork in 3 t 4 months

Good med l manageme t plies mprehensive care This and prompt re ol ion of la m (such as th Cardiac Board ad ises k se the need for work assessment cent l hen th patient resources are nd l me nd b d sab lities ndul great recou se t h t lities f comprehensive rehab lit t on serv nduc ted.

Modern rgers h k l se p ar ted the remediable from the perm l l l ked in the ongen tal and heumat ardi group It is in de ling ith these lases th t l d h l l tation techniques ret rn the gre st be n in lut ng educ tional nd social eta lat n nd superadded ardiac neu roses I rec t ar f rth group h emerged one h b is t et l le t rk but wh h not fficientl l sulded t mer pen-heart surgery The sal ging of these patie ts the ad ent of improv l surg l mea es l alluth surgery beth he for cong t l heumatic or coronary he rt disease merely ugme t this group

I he tt mpt t rehab litation there re cert in factors over h h the ph sicia has no ontrol. The l t of the aged nskilled worker ho is of limited telligence nd nnot be retrained depends entirely on the severit of his cardiac infarction. H might obta ork in factory if he would migr te t the city but social, family or often economic ties keep him in the country where suitable work is una ail ble Moreover compet tiv industries discriminate gainst males for the lighter types of ssembl or process work and ncreasing tomation ill make such orkers even more red nda t On the other hand, oman is usually able t manage her ow housework where time is not factor nd electric l ppliances and mecha ical ds can be afforded t lighten her tasks

Economic factors are importa t in determi ng patient motivation The young man with f mily responsibilities is positively motivated, hereas the older ma may be content to drift long assisted by Social Service benefit, supplemented by his f m ily earnings. The occasional worker has little t gain from ttempts t become self-supporting However t the present time it is ery difficult t find suitable light work for the middle-aged coronary patient in the provincial cities. This problem hould diminish w th the establishment of light industry and sheltered (terminal) workshops outside the metropolitan area. Although excellent in theory this concept will demand ery positive pol tical organization to reverse the present trend to the urbanization of manufact ring and the rationalization of rural industry

The heart has long been the cultural seat of ma y highly emotive disorders. The lay ocabulary of heart function is supercharged with passion and fear This fear infects the patient, his family and his doctor An accurate appreciation of prognosis in coronary heart disease ha not kept pace with the ulgariz tion of the electrocard graph The confusion of the patient is completed by the depersonali zation of the t aching hospital nd the inadequacy of the doctor ho l preoccupied exclusively ith scient fic spect of the dise se and is nwilling or too self-consciou t llow the patient t identify th him so that h takes respon ibility for the successf l outcome of the illness. The sorry chapter on long term anticoagula t of which the last word is not y t ritten indicates the global fear nd insecurity of the medical profession in this context. Whatever the final deci ion on this vexed question there is no doubt that in the face of so much medical d'fgeace rehabil tation becomes irtually impossible Positive medical management minimizes this problem, although small group ha remained hich resists all effort t reassure them These people are found to be using their cardiac dise se be t real or imaginary a mea of escape from some intolerable domestic or work ituation. Attempt t correct their ttitude usu lly mak them worse rather than better

It ha been show that certain factors, e g car diac neur is, are largely correctable by education nd good medical management Medicolegal maneu ers such setting up ell-conducted orkmen compensation tribunals, will prevent most of the long term problems ssociated ith the rehabilitation of the patient ith coronary heart disease E isting linical facilities (including the sophistication of many general pract tioners) should be adequat t prevent most of the rehabilitation problems that ould otherwise arise Cardiac surgery is lter ing some spects of congenital and rheumatic heart disease lthough it palliative side is ugment ng the number of those who surv l incapacitated A group remains in which the chief factor preventi g rehabili t tion is the insufficiency of suitable light work. E isting rehabil t tion serv ices are adequate t meet the present (slowly decl ning) demand for them. Sheltered orkshops are needed for those fit only for ork under noncompetitive conditions.

Insufficiency of suitable light ork is a funda mental on hich no medical social or political measures so far hav had any effect.

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Hereditary transmission of patent ductus arteriosus in the dog

In an epidemiologic study of congenital heart disease in dogs presented to a veterinary clinic of a large university patent ductus arteriosus was the cardiovascular defect most often detected. As in man the anomaly was found with greater frequency in females than males (Table I)

Among purebred dogs with congenital heart disease greater proportion of poodles, collies, and Pomeranians had patent ductus arteriosus than would be expected if all breeds were equally susceptible (Table II). This finding suggested that genetic factors might be important determinants of patent ductus in the dog

Three test matings of a male poodle, with surgically corrected patent ductus, to a female mongrel, with an untreated patent ductus, yielded a total of 12 pups. In 5 of these, patency of the ductus arteriosus was evident clinically and was confirmed at surgery (2 puppies) or by postmortem examination (3 puppies) after the time of normal closure (Fig 1) Functional patency was suspected in 2 puppies which died in the early neonatal period. No other cardiovascular malformations were evident clinically or on postmortem examination in any of the dogs.

These findings provide confirmatory evidence that patent ductus arteriosus is heritable in the dog

Table I Sex specific prevalence rates for patent ductus arteriosus and other cardiovascular malformations (University of Pennsylvania Veterinary Clinic, 1958 1965)

Sex	Number in population	Patent ductus arteriosus		Other malformations		All malformations	
		N	(Rate/1,000)	N	(Rate/1,000)	N	(Rate/1,000)
Male	19 263	28	1 4	99	5 1	127	6 5
Female	16 017	40	2 4	73	4 6	113	7 0
All dogs	35 280	68	1 9	172	4 9	240	6 8

*Significantly different (P .06)

Table II. Breed distribution of patent ductus arteriosus in purebred dogs with congenital heart disease (University of Pennsylvania Veterinary Clinic 1953-1965)

Breed	Number with patent ductus arteriosus	Number with other common malformations*	Total	Probability†
Poodle	20	4	24	P < 0.001
Collie	5	0	5	P = 0.001
Pomeranian	3	0	3	P = 0.036
Other purebred	40	132	172	
All purebred	68	136	204	

*Includes pulmonic stenosis, aortic stenosis, ventricular septal defect, persistent right aortic arch, and tetralogy of Fallot.
†In the case of poodles the probability of the observed or more extreme distributions was determined by the chi square test, under the hypothesis that among dogs with congenital heart disease poodles do not have a different proportion with patent ductus arteriosus than other purebred dogs as a group. For collies and Pomeranians the probability of the observed distributions (there are none more extreme in the same direction) was determined by the Fisher exact probability test (one-tailed) under the hypothesis that the breeds tested do not have a greater proportion with patent ductus arteriosus than other purebred dogs as a group.

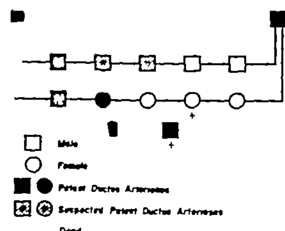


Fig. 1. Pedigree of 3 test matings between a male poodle with surgically corrected patent ductus arteriosus and a female mongrel with untreated patent ductus. The ductus arteriosus remained patent in 5 of 12 offspring and was probably functionally patent in 2 others which died in the early neonatal period.

and indicate that it will be possible to produce affected dogs by selective breeding. Such animals will be useful for the study of the underlying pathogenetic mechanisms in this anomaly.

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Bacteriuria and nonobstructive renovascular disease

The role which asymptomatic bacteriuria plays in the natural course of nonobstructive renovascular disease, and the role of the latter in the development of intrarenal infection has not yet been precisely defined.

Experimental data suggest that intrarenal vascular changes, whether associated with hypertension or not, increase the susceptibility of the kidney to infection. However, the increased renal susceptibility has not always been supported by clinical evidence. On the other hand, the clinical observation that chronic pyelonephritis is a cause of hypertension[4] has not always had its experimental counterpart. There is evidence that the experi-

mental hematogenous and ascending[16] pyelonephritis may not be morphologically identical entities or pathogenetically related to the kidney disease observed in human beings.[10] Since high blood pressure is predominantly human disease and since the various experimental models are not entirely relevant to the clinical problem further investigation in man is necessary to clarify the relationship between pyelonephritis, nonobstructive renovascular disease, and hypertension.[11,12]

The answer to the clinical problem will be provided from further detailed statistical survey concerning the frequency of bacteriuria in normotensive and untreated hypertensive populations. In parallel, the incidence rate of hypertension during the clinical course of pyelonephritis should be studied in various pyelonephritic groups, prior to the appearance of renal failure. Since the prevalence rate of bacteriuria and hypertension is higher among pregnant, elderly, diabetic, nephritic, nephrotic, and neurologically crippled persons, the conclusion that pyelonephritis has causal relationship to hypertension in these groups will be in doubt until proved by investigations of the incidence rate of hypertension in bacteriuric patients compared to suitably matched control subjects. These studies are even more essential because it is not yet proved that the association of bacteriuria with hypertension, even if it is shown to be one of cause-and-effect, is through the mechanism of chronic pyelonephritis. The problem of this association can be resolved in epidemiological studies because essential hypertension tends to be familial in prevalence whereas bacteriuria does not;[17] however, this question remains open in clinical practice. Brod[5] reported more hypertension in pyelonephritic patients with family history of hypertension than in those without such history. Furthermore, Cruz-Coke[14] reported that the relatives of patients with pyelonephritis and hypertension have higher diastolic pressures than do the relatives of patients with pyelonephritis but no hypertension.

In regard to the same question, the findings of the comparative epidemiological studies[3,14] indicate that, beyond the age of 30 years, the blood pressures of bacteriuric women tend to be higher than those of nonbacteriuric women, but that this trend disappears after the age of 60 years. Moreover, in another recent study, in which asymptomatic bacteriuria was detected in 23 per cent of a group of clinically healthy subjects over the age of 65 years, the prevalence of hypertension was not higher in the bacteriuric subjects. It is important that bacteriuric individuals, in addition to more advanced tubular impairment, had evidence of more pronounced intrarenal vascular changes. The significantly decreased glomerular filtration rate and renal plasma flow cannot be accounted for by the pyelonephritic process alone but by the superimposition of pyelonephritis upon nephrosclerosis, thereby accelerating the pre-existing vascular lesions.[12,13] In the bacteriuric sample the prevalence of hypertension did not differ enough, possibly because of nonsufficient ischemic tubular damage[12] to lead to renoprival hypertension.[11] In addition, increased levels of urinary lactic dehydrogenase activity in the group with bacteriuria suggest active renal involvement, and almost all theories on the pathogenesis of hypertension in pyelonephritis deny the role of the active bacterial infection of the kidney.

In conclusion, it must be re-emphasized that the relationship between bacteriuria, renal vascular disease, and hypertension needs to be further investigated by cooperative ventures in various populations.[17]

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Letters to the Editor

University of Pennsylvania
Philadelphia, Pa.
December 22, 1966

To the Editor:

Once again, the snark-like, supposedly unique zero of potential has been introduced into electrocardiography. This time it has been discussed in connection with maps showing equipotential contours on the body surface during the cardiac cycle ("Body Surface Isopotential Maps in Normal Children, Ages 4 to 14 years," by M. S. Spach, W. P. Silberberg, J. P. Boineau, R. C. Barr, E. C. Long, T. M. Gallie, J. B. Gabor, and A. G. Wallace, AMERICAN HEART JOURNAL 72:640, 1966). It is particularly ironic that the subject should be reintroduced in this context because isopotential maps provide a striking example of the uselessness of identifying a so-called zero line or any other absolute potential in electrocardiography.

Consider a map drawn for any instant during the cardiac cycle. By definition, an equipotential contour is a line drawn through points between which no difference in potential is developed at that instant. Clearly, the construction of such a line has nothing to do with the reference point chosen by the investigator in some intermediate step that he may have used to obtain his map. Differences among maps from the same subject at the same instant of the cardiac cycle could involve only the particular lines one chooses to draw and the numbers with which the lines are labeled.

The more lines used, the closer all such maps will be to each other in appearance. For example, if the maps are all drawn showing equipotentials at intervals of 0.01 mv. the level of quantization, the contours of the maps obtained would be virtually indistinguishable, no matter what the reference. When the level of quantization is increased and fewer lines are used, detail is lost and maps may look different because they will not necessarily show identical contour lines. Under these conditions, it is conceivable that uncertainties in the interpolation of contour lines between those actually shown may impede comparison of such maps. As long as a sufficient number of lines are drawn to convey the essential pattern, all maps provide equivalent information no matter what is used as a reference.

Altering the reference causes all numbers on a particular map to change by the same amount. Although adoption of a common reference appears to facilitate comparison of electrocardiographic maps among investigators, it has resulted, unfortunately, in the assignment of significance to the absolute value of a line rather than its contour and association with neighboring lines. The electrocardiographic data from which the map was constructed as well as any conventional or nonconventional surface lead, can be reconstituted from the map (within the limits of precision and accuracy available) regardless of the reference used. For this reason, the concept of an absolute potential—rather than differences in potential—is without meaning.

David B. Geselowitz, Ph.D.
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Stanley A. Briller, M.D.
Associate Professor of Medicine

Duke University Medical Center
Durham, N. C.
March 1, 1967

To the Editor:

We are indebted to Dr. Geselowitz and Dr. Briller for pointing out the implication they noted concerning our zero potential. We are in complete agreement with them that any absolute potential, including zero, is determined only by definition.

Although we are quite indebted to Dr. Geselowitz and Dr. Briller for pointing out any erroneous implication that a unique zero of potential was being derived, we think that designating some standard reference line, regardless of the label applied to it, is of practical importance. One can certainly deduce the difference in the two arbitrary constants when comparing two maps, but the labor required to then convert the maps to the same reference is considerable.

R. C. Barr, B.S.
Madison S. Spach, M.D.
John P. Boineau, M.D.
Theo C. Pilkington, Ph.D.

Demand pacemaker

To the Editor:

The demand pacemaker as described by Drs. Lemberg and Castellanos and their associates has certainly provided a dramatic new method of treatment of A-V block, particularly of the intermittent type. It has been emphasized that this pacemaker will escape whenever a preset asystolic interval has been exceeded and will automatically stop when a natural or artificial beat occurs at a faster rate.

In 1963 I had a chance to use this pacemaker when I was in the United States at the Heart Station of the Philadelphia General Hospital. It worked

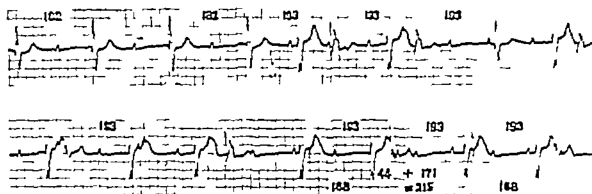


Fig 1

lmost ... k h ... lemand ... I experienced, however ... h ... Fig 1 ... er interesting ... h b the p... maker f ... ioned a ... trogenic para... tole ... h ... ou ... timulated the he rt ... he ... he direction of he main QRS omplexes of nat ... I b ... t ... udde ... hanged. This experience ... how ... tha ... atrogen ... pa ... s tole ... ccu ... even ... hen ... demand pacemaker is used if the direction of the main QRS omplexes of natural extras ... t ... les or the natur l rh thm ... re opposed t ... those of the preced g beat. I do not know whether the pacemaker has been improved t ... guard ag inst such ... dysf nction since I left the United St tes.

I ... m interested in this poi t ... nd I would lik ... to know the present tatus of the pacemaker ... nd of ... ny improvements.

M ... T ... M D
Cardiology branch
Department of Med ... ine
K ... Cit Hospital
K ... J ... pa

American Optical C ... Chelsea, Mass

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Reply

T ... th Editor

Thank you ... ery much for ... llowing me t ... omment on Dr T ... kagi letter t ... the ed tor

Dr T kagi ha ... properly ... nalyzed the lectrocardiographic trace. It is evide t that w th ... change n direction of the QRS complex t ... neg ti ... deflection, the demand pacemaker previously set t ... sense pos tive deflections now performs ... a continuou ... pacemaker. A pacemaker-induced ... entricular para ... ystole result. The third timulu ... artefact in the top trace fuses w th but does not effect the QRS complex.

The original demand pacemakers built int ... the bedside cardiac monitors sense the first deri ... tiv ... of either the positi ... or negative deflection of the QRS omplex but not both. A switch on the front panel of th ... nit can change the sensing from positiv ... to negativ ...

Dr T kagi may be interested t ... know that the prototype units of the new implantable miniaturized demand pacemaker now i ... clinical use in ou ... hospital sense both positiv ... and negati e deflections.

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Miami Fla

American Heart Journal

September 1967 Volume 74 Number 3

Editorial

Cardiovascular adaptations in diving mammals

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The seals (Pinnipedia) and the whales (Cetacea) are highly developed animals. The level of organization of their central nervous systems, especially that of the cetaceans, is unsurpassed among animals. The metabolic processes of their organisms proceed at a high rate, thus, seals and whales maintain body temperatures of 35 to 38° C.

Such specialized organisms are usually highly vulnerable to asphyxia. Acute respiratory arrest in man and most other air breathing vertebrates causes great discomfort, loss of consciousness, and convulsive efforts to breathe. If breathing remains obstructed, death is certain within a few minutes. However, the diving vertebrates are able to remain submerged for prolonged periods of time (15 minutes to 2 hours) without showing any motor disability upon emersion and yet they are equipped with essentially the same respiratory and circulatory organs as their terrestrial relatives. Moreover, it has been recorded that the Weddel seal *Leptonychotes weddelli* may dive as deep as 600 M. and indirect evidence indicates that the sperm whale *Physeter catodon* may descend to approximately 1,000 M. These depths are the deepest on record, but there are numerous reports in the literature of various species of vertebrate divers descending several hundred meters down in the oceans. The ability of homeothermic vertebrate divers to descend to great depths and remain under water for extended periods of time present the comparative physiologist with two formidable questions. These problems have been thoroughly investigated over the past 30 years, and the results are such that they may be of general interest to physiologists and physicians alike.

Prolonged diving

Since seals and whales are unable to extract oxygen from the water by means of accessory respiratory organs, they must depend on the oxygen stores within the body for aerobic metabolism when they are submerged. Estimates of the total amount of stored oxygen in diving mammals have shown that the oxygen deposits are larger in divers than in nondivers, but nevertheless are insufficient to maintain an aerobic metabolism at the prediving rate during a long submersion. The possibility of a switching from aerobic to anaerobic metabolism during diving has been suggested by several authors and investigated with various methods. Continuous registrations of oxygen consumption before and after diving have shown that the excess intake of oxygen after a prolonged, quiet, and restrained dive is much less than would have

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face these processes are reversed and decompression illness is avoided [7]

It may be said that the diving mammals are not in any danger of contracting the bends because they do not receive any supply of air at high pressure while submerged However it is well known that a series of repeated skin dives increases the possibility of decompression illness in humans. Moreover the incidence of caisson disease due to accumulation of nitrogen increases with increasing amounts of body fat since the fats are very good nitrogen solvents. For these reasons, diving mammals might well incur decompression illness were it not for the protective mechanisms discussed above

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Ectopic rhythms originating anteriorly in the left atrium

Analysis of 12 cases with P-wave inversion in all precordial leads

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Much evidence now favors the concept that the left atrium plays an important role in the formation of ectopic impulses in man.[1-4] This evidence was obtained mainly by vectorial analysis of atrial deflections in routine scalar electrocardiograms. More recently, experimental observations consistent with the electrocardiographic considerations also became available.

The aim of the following communication is to draw attention to a distinctive and hitherto undescribed form of left atrial rhythm characterized by inversion of the P waves over all of the precordial leads. In contrast to previously reported instances of left atrial arrhythmias, whether of normal[1-3] or of rapid rate, in which the pacemaker was localized in the posterior part of the left atrium, in the variant under discussion the initiating focus seems to be located in its anterior portion. This type of ectopic rhythm was commonly misinterpreted either as sinus rhythm or as nodal rhythm, depending upon the high or low location of the pacemaker. Twelve such cases have been found in the files of the Division of Cardiology of this institution and are the subject of the present analysis.

A preliminary report of this work has been published in the form of an abstract.

Clinical data

The electrocardiograms upon which this report is based were form 12 patients, 10 males and 2 females whose ages ranged from 13 to 93 years. All of these patients presented evidence of some structural alteration of the cardiovascular system. There were no cases of dextrocardia in this series. Only 3 patients were receiving digitalis at the time the recordings were made. The relevant clinical findings are listed in Table I.

Electrocardiographic data

All of the available electrocardiograms were reviewed. The tracings were recorded by a one-channel direct writing electrocardiograph (Sanborn or Focuda). The amplification used was that of 1 mv. = 1 cm. The routine electrocardiographic measurements were made according to standard procedures. The direction of the mean frontal and horizontal P vectors has been estimated by inspection, taking into consideration the net areas enclosed by the atrial deflections. The horizontal lead reference frame employed in this study

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Table I Clinical data

Case number	*Sex*	*Age*	*Blood pressure (mm Hg)*	*Digitalis*	*Cl ical diagnoses*
1	M	69	220 130	N	Hypertensi e cardiov scular disease
2	M	59	185 85	N	Bac llary dysentery tat after m ocardial I f rction
3	M	51	180 120	Yes	Chronic cor pulmonale ongesti he rt failure
4	M	73	145 70	N	Arteriosclerotic heart disease my cardial infarct on
5	M	55	220 130	N	Hypertensiv cardiov scular disease
6.	M	18	120/ 0	No	M tr l I fficiency aortic tenosis
7	M	73	180 110	Yes	M ocardial I fraction, hronic cor pulmonale
8	M	13	90 70	N	Mit l Insufficiency
9	M	75	180/100	Yes	Myoc rdial nfarction heart f ilure
10	M	5	150/100	No	Myocardial f rction
11	F	52	140 100	N	Coronary insufficiency diabetes mellitus
12	F	50	160/100	No	Myocardial farction hypertension

Table II Electrocardiographic data

Case number	*Rhythm*	*Date of record*	*Rate (per min)*	*P R (sec)*	*P R index*	*P waves: Duration (sec)*	*P waves: Voltage (mv.)*	*P waves: Lead I*	*P waves: ÂP (degree)*
1	LAR	Nov 18 1952	65	0 15	0 75	0 09	+0 15	+	+80
2.	LAR	Oct 3 1955	105	0 12	0 66	0 06	+0 15	+	+80
3	LAR	March 27 1960	95	0 14	0 73	0 08	+0 15	−+	+90
4	LAR	Sept. 23 1963	80	0 13	0 65	0 06	+0 10	−+	+90
	Si us	Sept 11 1963	57	0 16	0 76	0 07	+0 10	+	+75
5	LAR	April 10 1956	90	0 12	0 60	0 08	+0 10	−+	+30
	Sinus	M y 24 1956	80	0 16	0 80	0 11	+0 10	+	+30
6.	LAR	July 15 1965	80	0 14	0 73	0 09	−0 25	−+	−90
7	LAR	June 5 1962	80	0 14	0 70	0 08	−0 30	+	−80
	Sinus	M y 24 1962	90	0 16	0 80	0 10	+0 30	+	+75
8.	LAR	M y 5 1965	80	0 16	0 93	0 05	+0 10	−	−100
	Sinus	April 18, 1965	80	0 18	1 05	0 06	+0 15	+	+70
9	LAR	M rch 29 1966	60	0 09	0 42	0 08	+0 10	+	−75
	Sinus	M rch 29 1966	60	0 12	0 57	0 08	+0 10	Und	0
10.	LAR	Dec 11 1963	75	0 14	0 70	0 08	+0 10	+	−75
	Sinus	Dec. 15 1963	83	0 14	0 70	0 08	+0 10	+	0
11	LAR	April 28, 1966	110	0 08	0 44	0 06	−0 25	−	−120
12	LAR	J ne 14 1966	75	0 12	0 60	0 06	+0 15	−	−100
	Sinus	J ne 29 1966	78	0 15	0 75	0 10	+0 10	+	0

LAR: Left atrial rhythm. *Und* Undetermined. *ÂP*: Mean frontal P vector *P-R index*: A ratio between the P R interval as measured from the tracing (numerator) and the pper lim of normal A-V conduction ime for the given age and heart rat (denominator)

has been described elsewhere In addition to the conventional measurements of the P R interval the duration of the atrioventricular conduction time was evaluated also in terms of the P R index.[11,13] The relevant electrocardiographic features are summarized in Table II

Atrial activation in the frontal plane leads According to the polarity of the P waves in Leads II III and aVF our material was divided into two groups Group A, initially interpreted as showing sinus rhythm (5 cases) with upright P waves in Leads II III and aVF (Figs 3 4 and 6) and Group B initially interpreted as showing either nodal or coronary sinus rhythm (7 cases) with inverted P waves in Leads II III and aVF (Figs. 8 and 9)

There were no cases with P wave inversion in Lead I in Group A In 3 cases the P waves were biphasic with initial negativity (−+) in this lead In Group B 3 cases exhibited inverted P waves in Lead I In one case the P waves were biphasic (−+) and in another one the P waves although upright had a clearly visible initial negativity Thus, a total of 8 of the 12 cases showed evidence in Lead I of an initial or average rightward direction of atrial activation.

The direction of the mean frontal P vectors is shown in Fig 1 It can be appreciated that with the exception of Case 5 located at +30 degrees in the frontal reference frame all vectors are grouped in two narrow areas those of Group A between +80 and +90 degrees, and those of Group B between −75 and −120 degrees.

Atrial activation in the horizontal plane leads In all cases, by definition the P waves were inverted in the precordial leads, from V to V₆. This feature prevented an individual determination of the direction of the mean horizontal P vectors. However it was possible to determine the range of distribution of the horizontal P vector for the whole series. It is evident from Fig 2 that in order to be projected on the negative halves of the Leads V_1 and V axes this vector has to be located beyond the −90-degree position to the left and beyond the −1 0-degree position to the right in the horizontal reference frame Such positions ma be fixed arbitrarily a

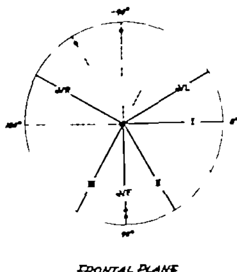


Fig 1 Direction of the mean P vectors in the horizontal plane.

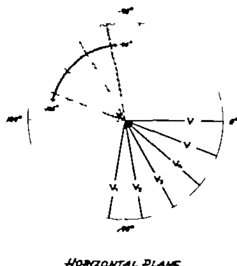


Fig 2 Distribution area of the direction of the mean P vectors in the horizontal plane (between −95 and −165 degrees) The horizontal lead reference frame employed in this study has been reported elsewhere.

−95 and −165 degrees respectively a range which indicates an average posterior and rightward direction of atrial activation

Spatial direction of atrial activation On the basis of the data presented above it is possible to conclude that the mean P vectors in Group A are spatially directed

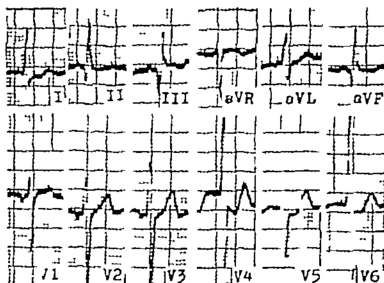


Fig. 3. L nal b hm (C se 2) Not in erted precordial P es. Electrocardiogram initially interpreted sho s h thm

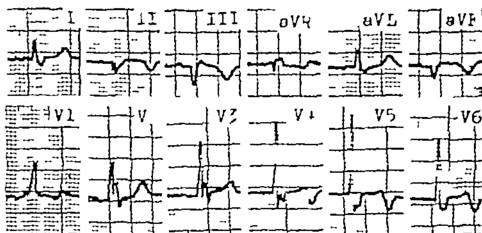


Fig. 4. Left trial rhythm (Case 4). N t in erted precordial P w es nd initial negati ity of the P w in Lead I. Electrocardiogram initially interpreted a showing si us hythm. Compare with Fig. 5.

downward to the right and posteriorly and that in Group B they are directed upward to the right and posteriorly. If it is assumed that the negative extremity of these vectors indicates approximately the area in which the impulses originate the pacemaker in Group A is located superoanteriorly in the left atrium and that in Group B is located inferoanteriorly in the left atrium.

Atrioventricular (A V) conduction. The A V conduction time was either normal or short.

Sinus rhythm. In 2 cases of Group A and in 5 cases of Group B tracings with sinus rhythm were also a ailable for analysis. The A V conduction time in these tracings was usually longer than in those with ectopic rhythm.

Discussion

The electrocardiographic expression of left atrial automaticity has been exten sively studied n the past few years, and several distinctive patterns have been described.[1-4] These tudies indicated the

posterior portion of the left atrial wall as the area in which the ectopic beats were initiated. The fact that permanent cardiac pacemakers may also be located anteriorly in the left atrium is strongly suggested by this communication.

The presence of inverted P waves in all of the precordial leads from V_1 to V_6 inclusive is the common and outstanding feature of the tracings upon which this report is based. A clear understanding of the genesis and significance of such changes becomes possible when one recalls that the form and polarity of atrial deflections is determined by the direction and order in which the atrial tissue passes into the active state and that a negative deflection appears in a unipolar lead when the activation wave is moving away from the exploring electrode.[11] The application of these principles allows two conclusions to be drawn. (1) The activation wave in our cases spreads backward moving away from the anterior chest wall explored by Leads V_1-V_4. (2) The same excitatory process progresses also in a left-to-right direction moving away from the left axilla explored by Leads V_5 and V_6. Since the site of formation of impulses is by definition the first area activated, the logical implication is that the pacemaker is located somewhere anteriorly in the left atrium.

A more precise spatial localization of the site of origin of the impulses can be achieved by an additional analysis of the extremity leads. Although the precordial leads offer information concerning the direction of electrical forces along the transverse (X) and the sagittal (Z) coordinate axes of the body,[18] a knowledge about the phenomena reflected by the vertical (Y) coordinate axis is provided by the polarity of the P waves in Leads II, III, and aVF. In this respect it appears that our material is not homogeneous: cases in Group A (upright P waves in Leads II, III, and aVF) have their pacemaker located high in the atrium, whereas cases in Group B (inverted P waves in Leads II, III, and aVF) have the impulses originating low in the atrium.

Vectorial approach synthesizes concisely all of this information. Since the spatial orientation of the mean P vector represents the average direction of atrial activation, the negative extremity of this vector approximately indicates the area in which the cardiac stimuli originate.

In principle, this approach seems to be both rational and simple but also has its limitations because of several factors such as errors in computing the direction of atrial vectors, inherent characteristics of the lead axes systems, the complex geometry of the atria, their asymmetrical orientation within the chest, the presence of concomitant hypertrophy or dilatation of one of the atria, etc. The errors involved, however, appear to be of little practical significance since the vectorial method under consideration aims only at indicating *the area* in which the pacemaker *most probably* originates and is not intended to pinpoint precisely the actual site. For example, whether the direction of a mean P vector in the frontal plane is +95 or +70 degrees, the deduction made will be the same, namely, that the frontal P vector points downward. By the same token, the relevant information inferred from a +120-degree position of this vector in the horizontal plane will be similar to that inferred from a +140-degree position, namely, that the horizontal P vector is directed anteriorly and to the right. Since the vector under discussion points spatially downward, anteriorly, and to the right, the conclusion that the focus of formation of impulses in this case is most probably located somewhere superiorly and posteriorly in the left atrium appears to be justified.

Another factor of particular theoretical importance is represented by the presence of intra-atrial conduction disturbances which could account for a more or less pronounced deviation of the resulting vector. However, the meager evidence available at present for the very existence of such disturbances in clinical conditions makes this possibility purely hypothetical.

It is important to point out that cases included in Group A were initially interpreted as being examples of sinus rhythm. This diagnosis was based upon the fact that the atrial rate, the A-V conduction time, and mainly the P wave polarity in the extremity leads were all within normal limits. little attention, if any, was paid to

the inverted precordial P waves. Indeed although the presence of upright P waves to the left of Lead V in sinus rhythm is occasionally acknowledged, P wave inversion in these leads has not been considered, to the best of our knowledge, as being incompatible with this diagnosis. However, the anterior and leftward spread of atrial activation which characterizes sinus rhythm cannot possibly give rise to P wave inversion in all of the precordial leads, and the presence of upright precordial P waves from Lead V to the left has to be accepted as a sine qua non for the diagnosis of sinus rhythm.

It is particularly pertinent to the present discussion that in 2 patients in Group A, in addition to electrocardiograms exhibiting the interior variant of left atrial rhythm (Figs. 4 and 6), tracings displaying true sinus rhythm (with upright precordial P waves) were also available (Figs. 5 and 7). Although both types of electrocardiograms might have been diagnosed as examples of sinus rhythm on the basis of the findings observed in the extremity leads, the discordant polarity of the atrial deflection in the precordial leads, the different form of the P waves in the limb leads, and the variation in the AV conduction time clearly indicate the presence of two different pacemakers. Obviously only one of these can be a sinus pacemaker and, as stressed above, it has to be the one which displays upright precordial P waves, whereas a different location has to be considered for the other pacemaker.

By the same token, cases included in

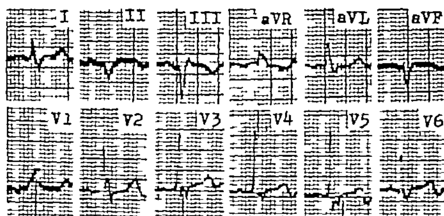


Fig. 5. Electrocardiogram of the same patient as in Fig. 4 exhibiting sinus rhythm. Note upright precordial leads from V to V ... ell ... In Lead I. The P-R interval is 0.16 second, compared to 0.13 second in Fig. 4.

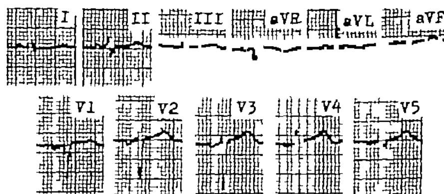


Fig. 6. Left atrial rhythm (Case 5). Note inverted precordial P waves. Tracing initially interpreted as showing sinus rhythm. Compare with Fig. 7.

Group B were previously diagnosed as being examples of nodal or coronary sinus rhythms (Figs 8 and 9) The classic criterion for these arrhythmias namely the presence of retrograde P waves in Leads II III and aVF was fulfilled entirely However atrial activation in rhythms arising in the area of the A V node progresses from right to left whereas its direction in the cases in Group B was as demonstrated, from left to right. It is this evidence of an average rightward direction of atrial activation which virtually eliminates the possibility of origin of impulses in the right atrium whether in the sinus node in the area of the A V node or in the area of the coronary sinus.

This report illustrates well the limitations of the conventional approach to the diagnosis of atrial rhythms. These limitations, discussed in detail in a previous communication [3] stem for the most part

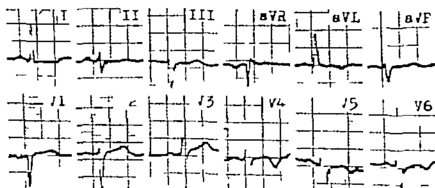


Fig 7 Electrocardiogram of the same patient as in Fig 6, exhibiting sinus rhythm. Note upright precordial P waves from V to V The P-wave configuration in the extremity leads is different than in Fig 6, and the P R interval is longer (0.16 second as compared to 0 12 second)

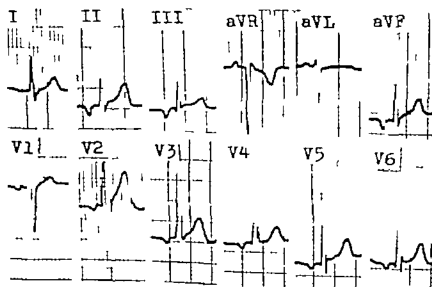
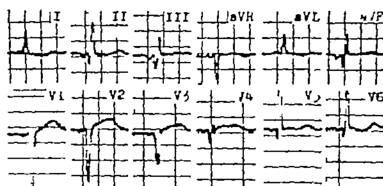


Fig. 8 Left atrial rhythm (Case 6) Note inverted precordial P waves and initial negativity of the P wave in Lead I Tracing initially interpreted as showing coronary sinus rhythm or eventually upper nodal rhythm with block.

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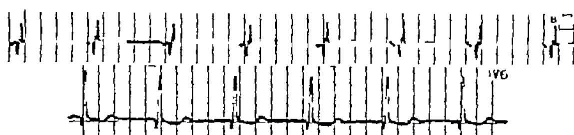


Fig. 9. [illegible] precordial leads [illegible] interpreted [illegible] showing [illegible] strip of Lead V[illegible] shows spontaneous [illegible] from left atrial rhythm [illegible] long strip of Lead V[illegible] shows [illegible] from [illegible] rhythm [illegible] left atrial rhythm in the same patient.

from the usual custom of analyzing arrhythmias almost exclusively in the extremity leads. In fact, such leads form an imperfect bidimensional reference system which explores only the frontal plane of the body and is thus inherently unsuitable for the study of spatially oriented electrical phenomena. The localization of the atrial vector in space, a prerequisite for any rational attempt to identify the site of origin of impulses, requires the knowledge of its three mutually perpendicular components. In theory, the frontal lead system yields information on only two such components, the transverse and the vertical ones. In practice, however, the usefulness of the extremity leads in this respect is even more limited than expected from theoretical considerations. It has been shown recently that the direction of the transverse component of the atrial vector cannot always be inferred faithfully from P wave polarity in Lead I. Although this fact is usually of little practical interest in clinical electrocardiography, it becomes significant when the demonstration of an average left-to-right spread of atrial activation is diagnostic of left atrial rhythms. On the other hand, since the direction of atrial activation along the transverse axis is easily inferred from the precordial leads, vectorial analysis of atrial deflections in these leads must become routine procedure if the correct diagnosis of a supraventricular arrhythmia is to be made.

It is noteworthy that this electrocardiographic interpretation is in keeping with modern physiologic knowledge concerning cardiac automaticity. The recently developed technique of intracellular recording by means of microelectrodes permits the definition of cardiac automaticity in the precise terms of electrical characteristics of single cells.[11] It has been shown that the property of automaticity belongs to specific automatic cells which manifest spontaneous depolarization during diastole. It is implicit in this approach that only areas of the heart which contain such automatic cells can be regarded as being an actual or potential pacemaker. In so far as the left atrium is concerned, it is probable according to Hoffman and Cranefield[7] that automatic cells are located at the junction of the pulmonary veins with

the atrium and in the left A V ring. This electrophysiologic localization is of great significance since it shows a remarkable agreement with the data indicated by vectorial analysis.

Another striking finding revealed by the microelectrode studies is the absence of automatic cells in the A V node. In fact, such a finding questions the impulse-forming function of the A V node, hitherto one of the most firmly established electrocardiographic dogmas. The need for determining the nature of arrhythmias usually referred to as nodal rhythms becomes a logical corollary of this discovery.

The concept of left atrial arrhythmias offers at least a partial answer to this problem. It appears to be clear from evidence presented in this and in a previous paper, as well as from experimental studies in progress, that many of the so-called nodal rhythms originate in the left atrium. This conclusion is also consistent with an old experimental observation that during A V rhythms the left atrium is usually activated and contracts before the right one.[17] However, were the pacemaker in these ectopic rhythms located in the A V node, it would be more logical to expect an initial activation of the right atrium or at least a simultaneous activation of both rather than initial activation of the left atrium. The postulation of the existence of special connections between the A V node and the left atrium which are supposedly shorter or conduct faster than the connections between the A V node and the right atrium,[7] in order to explain this phenomenon, is no longer necessary at a time when the very automaticity of this node appears to be questionable.

A reassessment of the respective criteria for the diagnosis of left atrial rhythms on the basis of the present material leads to conclusions which corroborate those stated in an earlier communication. The fact that only 3 cases in the present series exhibited inverted P waves in Lead I demonstrates that, in the majority of instances, left atrial rhythm cannot be recognized on the basis of P wave inversion in this lead. It should be noted, however, that in 5 other cases the P waves in Lead I were biphasic with initial negativity (−+). If one accepts such an initial negativity as indicative of initial left atrial activation, a supposition which seems to be well founded, the value of P wave configuration in Lead I in the diagnosis of left atrial rhythm would be somewhat increased.

On the other hand, the P wave inversion in Lead V appears again to be the most sensitive and the most specific sign of left atrial rhythm. As would be expected, the "dome and dart" P waves were not observed in this series; such distinctive P wave configuration is inherently related to a particular posterior location of the pacemaker in the left atrium and, consequently, cannot appear in anterior left atrial rhythms. Actually, in the presence of P wave inversion in Lead V₆, it is the polarity of P waves in Lead V which differentiates schematically the anterior type of left atrial rhythm from its posterior variant.

Although a discussion of the etiological aspects of left atrial rhythm is not within the scope of this paper, the fact that all 12 patients suffered from organic heart disease characterized by some hemodynamic overload of the left atrium (Table I) is probably worthy of note. Although the sample studied is too small to warrant any conclusions on etiology, the possibility of a relationship between left atrial ectopic activity and structural or hemodynamic alterations of the left atrium deserves consideration.

Summary

Twelve cases of a distinctive and hitherto undescribed form of left atrial rhythm, characterized by inversion of the P waves in all of the precordial leads, are presented. In contrast to previously reported instances of left atrial arrhythmias in which the pacemaker was located in the posterior part of the left atrium, in the variant under discussion the initiating focus was localized in its anterior portion. This type of ectopic rhythm was previously diagnosed as either sinus rhythm or nodal rhythm, depending upon the high or low location of the pacemaker.

The limitations of the conventional approach to the diagnosis of atrial rhythms responsible for this misinterpretation are discussed. It is emphasized that vectorial

analysis of P waves both in the extremity leads and in the precordial leads is essential for the correct diagnosis of supraventricular arrhythmias.

Experimental and electrophysiologic evidence in support of the concept of left atrial arrhythmias is presented.

The electrocardiographic criteria for the diagnosis of left atrial rhythm are discussed. It is pointed out that P wave inversion in Lead V₆ is the most sensitive and the most specific sign of this arrhythmia. In the presence of inverted P waves in Lead V₆, upright P waves in Lead V₁ indicate the posterior type of left atrial rhythm, whereas inverted P waves in Lead V₁ indicate its anterior variant.

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Myocarditis in young military personnel

Herpes simplex trichinosis meningococcemia, carbon tetrachloride and idiopathic fibrous and giant cell types

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Sudden death in previously healthy young adults may often be caused by clinically unrecognized myocarditis. Similarly the disease may occur as a severe exacerbation in some systemic illness. The autopsy incidence of myocarditis is perhaps as high as the 4 to 9 per cent reported by Saphir[1] who felt that the lesions were focal and therefore not seen on random sections. Our report concerns 9 unusual cases of myocarditis in young military personnel in whom heart disease either developed without clinical recognition as part of their terminal illness, or caused sudden unexpected death

To the clinician, the term myocarditis sometimes implies an infectious cause, but, to the pathologist, it implies any disease characterized by an inflammatory cellular infiltrate in the heart. As in our cases, the pathologist customarily excludes arteriosclerotic congenital and hypertensive heart disease and a history of chest trauma. Myocarditis may be arranged in the following general categories

Infectious and contagious myocarditis (may include some hypersensitivity reactions)
- Bacterial
  - Case 1 case 2 meningococcemia Waterhouse Friderichsen syndrome
- Viral
  - Case 3 herpes simplex
  - Case 4 chickenpox
  - Case 5 cause unknown, presumed viral
- Rickettsial
- Parasitic and miscellaneous
  - Case 6 trichinosis

Isolated or idiopathic myocarditis
- Diffuse
  - Case 7 chronic fibrosing myocarditis
- Granulomatous
  - Case 8 granulomatous giant cell myocarditis
- Myogenic giant cell type

Physical, toxic and metabolic myocarditis
- Case 9 carbon tetrachloride poisoning

Other myocarditides
- Rheumatic myocarditis
- Collagen vascular diseases
- Sarcoid
- Allergic and hypersensitivity types

Clinical manifestations and pathologic findings

The clinical criteria for the diagnosis of myocarditis, according to the New York Heart Association are as follows sinus tachycardia in excess of temperature rise abnormal rhythm enlarged heart a sys-

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tolic murmur at the apex usually that of mitral insufficiency though actually caused by left ventricular dilatation faint first heart sound of poor quality evidence of cardiac insufficiency electrocardiogram with atrioventricular or intraventricular conduction defect or ST T wave change fever and leukocytosis House[3] reported progressive myocardial failure tachycardia cardiac enlargement cyanosis low blood pressure and a rapid suddenly fatal course in cases of diffuse interstitial myocarditis. de la Chapelle and Kossmann regard vague aches and pains over the precordium weakness and fatigue a very significant in the patient with heart failure of unknown cause.

The pathologic findings in acute myocarditis are a dilated soft flabby heart with a pale red or a yellow-gray myocardium The edema and breakdown of myofibers result in a uniform homogeneous appearance to the myocardium In chronic myocarditis diffuse scarring is seen indistinguishable from that of arteriosclerotic origin The microscopic lesions vary from discrete abscesses to confluent areas of diffuse or interstitial myocarditis. Despite different etiologies, if the myofiber is deprived of oxygen or certain enzyme systems are poisoned or disrupted a sequence of cloudy degeneration fatty metamorphosis, fiber necrosis inflammatory infiltrate and eventual replacement by fibrous tissue ensues.[1]

Infectious and contagious myocarditis

Myocarditis due to meningococcemia.

CASE 1 J H was 22 year-old Negro recruit hospitalized with malaise, lethargy and fever of 12 hours duration While undergoing examination he complained of chest pain W thin moment he had convulsive seizures and then collapsed nd died.

At autopsy the heart was normal except that th myocardium *was of uniform ppearance and some*what red.

Microscopic examination revealed moderate dif fuse interstitial edema nd infiltrat of hronic in flammatory cells with some areas of myofiber fragmentation and degeneration with a general increase in size of myofiber nuclei Some capillary thromboses were present (Fig 1).

Other findings er enlarged edematous lungs with intra-alveolar hemorrhage a liver with moderat focal f tty metamorphosis enlarged adrenals with extensiv cortical and some medullary hemorrhage Inflamed meninges with some fibrin deposition and slight subarachnoid occipital hemorrhages widespread small vessel thrombosis and endothelial proliferation most prominent in the adrenals the heart the lu gs the kidneys and the brain Culture of blood and cerebrospinal fl id (CSF) *grew Neisseria meni gitidis* (Group B).

Th final pathologic diagnosis was septicemia due t *Neisseria meni gitidis* Group B ith hemorrhage of adrenal cortex

CASE 2. E. R., 19-year-old Caucasia recruit, wa admitted because of fever general malaise, backache and pain in the limbs of 2 days duration The temperature as 103 F the pulse 110 nd w ak, the blood pressure 70/40 mm Hg The skin had poor turgor and showed a few petechiae. The heart was not enlarged There were r pid but regular heart sounds There w bilateral conjunctivitis nd diff se pharyngitis Laboratory data included whit cell count of 3 700 with 39 per cent neutrophils, 40 per cent lymphocytes nd 1 per cent monocytes. Hematocrit was 43 per cent. The patient rapidly deteriorated int coma and repeated crops of petechial rashes appeared over the chest, abdomen, and extremities. Chest roentgenogram revealed haziness in the right upper lobe. Spinal fluid contained 19 mg per cent total protein and a cell count of 25 th 19 polymorphonuclear leukocytes and 6 lymphocytes. He was treated with intra enous sulfisoxazole, tetracycline and hydrocortisone. Shock developed and he was given intravenous levarterenol. He remained in shock and died 10 hours after admission

At autopsy the heart showed numerous epicardial nd endocardial hemorrhages up to 8 mm. i diameter and a diffuse interstitial round cell infiltrate of minimal to moderate degree with slight amoun t of interstitial edema (Fig 1).

There were numerous hemorrhagic areas in the skin mesentery nd bladder edematous hyperemic lungs with transudate filled alveoli adrenals ith hematoma and meninges with edema nd moderate inflammatory infiltrate small essel thrombi in the adrenals the lungs, the kidney the liver the brain nd the spleen. A temortem blood culture grew *Neisseria meningitidis* (Group B).

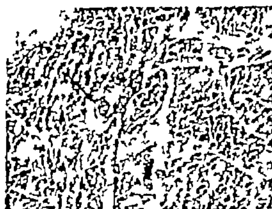


Fig 1 Case 1 Waterhouse-Friderichsen syndrome, small essel thrombosis, (see arrow) and diff se interstitial myocarditi most marked in the inter fascicular spaces. (× 100)

The final pathologic diagnosis was *Neisseria meningitidis* septicemia with bilateral adrenal hemorrhage.

Myocarditis associated with herpes simplex meningoencephalitis.

CASE 3. This 39-year-old Caucasian soldier was admitted because of seizures. The patient had been drinking heavily during the week prior to admission. Physical examination revealed an unresponsive, well-developed man with temperature of 104 F, a pulse of 100, and blood pressure of 120/90 mm. Hg. The neck was held rigidly. The conjunctivae were icteric. Examination of the lungs revealed diffuse rhonchi. The heart was normal. Neurologic examination revealed bilateral grasp reflexes and extensor plantar responses. Pertinent laboratory data included white cell count of 10,800 with 75 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes, 1 per cent monocytes, and hematocrit of 45 per cent. CSF showed sugar 99 mg. per cent, chloride 113 mg. per cent, total protein 51 mg. per cent, and cell count of 104 with 5 polymorphonuclear leukocytes, 74 lymphocytes. Subsequent examinations of the CSF during the patient's 11 days of hospitalization all yielded abnormal results. The white cell count rose to 20,000 with 74 polymorphonuclear leukocytes and 26 lymphocytes. In the hospital the patient, at first, was thought to be having seizures caused by withdrawal of alcohol. The CSF findings, however, confirmed viral encephalitis. The patient was treated with diphenylhydantoin and phenobarbital, but the seizures continued. On the third day intravenous penicillin was begun, but there was no change in the patient's condition. Liver chemistry studies revealed acute injury. On the sixth hospital day the patient passed 2 to 3 guaiac positive stools and was becoming dehydrated. He continued a downhill course marked by continuing severe seizures, the onset of bilateral pneumonia, and further gastrointestinal bleeding, that required the administration of 3 units of whole blood. On the eleventh hospital day the patient was noted to be hypotensive, with blood pressure of 65/40 mm. Hg. The pulse was 130. The urine output decreased and the patient died in spite of vigorous vasopressor therapy.

At autopsy the heart showed pale flabby ventricular myocardium with 2 small subepicardial scars measuring 3 mm. in diameter and extending 6 mm. into the anterior left ventricle; the coronary vessels were patent but had many focal atheromatous plaques.

Microscopic examination revealed many areas of myofiber degeneration and diffuse interstitial infiltrate of plasma cells, lymphocytes, and some neutrophils with marked increase of cardiac and tissue histiocytes (Fig. 2).

Other autopsy findings were scattered areas of acute and chronic necrotizing bronchopneumonia, perforated duodenal peptic ulcer with massive gastrointestinal hemorrhage, chronic non-specific pericholangitis and slight hepatic fatty metamorphosis, acute splenitis, diffuse meningoencephalitis with perivascular cuffing and gliosis and acute hemorrhagic necrosis of right and left temporal lobes, diencephalon, and pituitary gland.

The pathologic diagnosis was probable widespread viral illness. Postmortem lung culture revealed heavy growth of *Pseudomonas aeruginosa*. Blood and spinal fluid cultures revealed no growth. Acute and convalescent serologic studies revealed greater than fourfold rise in antibody titer to herpes simplex. Re-examination of the slides of the central nervous system showed Cowdry type A nuclear inclusion bodies suggestive of herpes simplex.

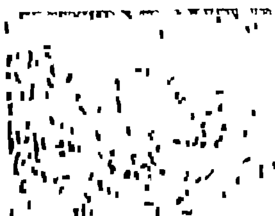


Fig. 2. Case 3, herpes simplex: swollen myofiber nuclei, and scattered inflammatory infiltrate with fibrosis and hyperemia. (× 240.)

Disseminated chickenpox with myocarditis

CASE 4. This 18-year-old Caucasian enlisted woman entered the hospital with a chief complaint of fever to 102° F. of 6 days' duration. Previous therapy consisted of oxytetracycline and aspirin. She had generalized aches and pains and pimples on her face and chest. The patient denied ever having had chickenpox. Physical examination revealed difficulty in swallowing, generalized skin lesions in crops appearing as papules, vesicles, and pustules with crusting. The temperature was 104.6° F., the pulse 100. The urine contained 1+ protein, bile, occasional red cells, and rare white cells. Hospital therapy consisted of oral and topical chlortetracycline and gentian violet. The temperature remained elevated, the sclerae became icteric and the liver was 5 cm. below the right costal margin on the fifth hospital day. Results of liver function tests were abnormal, with serum bilirubin 6.8 mg. per cent total, with 4.9 mg. per cent direct reacting bilirubin, thymol turbidity 22 units, and total serum protein of 6.8 Gm. per cent with 3.9 Gm. per cent globulin. The skin lesions were interpreted as varicelliform eruption. On the ninth hospital day the patient became semicomatose, passed a large black foul stool, lapsed into Cheyne-Stokes respirations, and died.

At autopsy the heart revealed a few hemorrhages along the left and right circumflex branches of the coronary arteries, which were otherwise normal.

There were scattered areas of interstitial lymphocytes, histiocytes, and plasma cells surrounding myofibers which showed cloudy degeneration and myofiber fragmentation with moderate interstitial edema (Fig. 3).

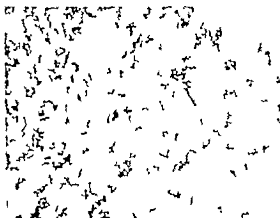


Fig 3 C se 4 h k p x (H er tial m carditis th hrm h flamma ry f fit t nd m ofibers x (X 110)

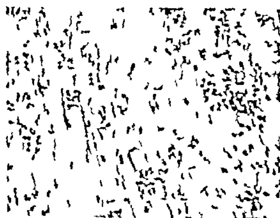


Fig 4 Case 5 probable ral pneumoni diffuse interstitial myoc rditis th bronc nd acut in flammation and focal degeneration of m ofibers. (X 240)

Other signific t autops findings ere the skin with generalized maculopa t la rash jaundice nd ulcers of mucous membranes enlarged hyperemic lungs with subpleural petechiae nd sc ttered necrotic foci of pneumonia 3 100 gr m soft li er th extensiv periportal and midzonal necrosis the ad renals, the spleen and the ov ries had necrotic foci Numerous sections of skin esicles ere consistent with aricelliform lesions. There as no postmortem ural growth on chick horioallantoic membrane, human epithelial (KB) or human fibroblast tissue cultures.

The final pathologic diagnosis hickenpox ith interstitial myocard tis.

P eumonia with myoc rditis

CASE 5 This 20-year-old Caucasian single ecruit developed pleuritic pain in the right side of the hest after 2 eeks of a mild productive cough Phy ical examinat on revealed an elev ted pulse and temper ture of 102° F th normal blood pressure and rapid painful respirations. The lungs had diminished breath sound t the right side of the base ith associated d llnes t per us ion. The heart as normal except f r tach ardia Laboratory studies rev ealed normal rinal i hemoglobin 11 gm per 100 ml., hit ll ou t of 16,200 with 80 poly morphonuclear leuko tes and 6 band ell nd 12 per cent typical lymphoc ytes Subsequent bl od ou t were 44,000 nd 6 ,000 th similar differentials. Chest roent genogr m rev led infilt t t the right base and small right pleur l effusion This later became mor extensi nd w soc iated ith an early left ostophrenic angle filtrat At thoracentesis, 3 5 of fibrin opalescent fluid ere drained and yielded no growth on ba t rial culture Oxygen as administered t relie the patient intense dyspnea and he trea ed ith hea y dosages of penicillin, hlor mphen ol kanamycin sulf t and intra enous ortisone H became more d spneic nd not lapsed int coma, nd died on the fourth hospital da

At tops the peric rdium contained 25 of slightl loud ellow flu) There as diffuse terst tial round cell infiltrat ith scattered reas of necrosis nd marked pink h line degeneration of m ofibers here ma y poly morphonuclea leuko tes nd eosinoph ls ere present Fragmentation nd loss of striation nd interstitial edema ith rare rdiac histioc tes were present (Fig 4)

Other ut ps findings ere massiv pleu al ef fusions th th k ellow purulent exudat over both lung surfaces nd extensiv interstitial pneumonia acut splen tis and 2,200 gram liver show ng bronic passi congestion nd acute inflammatory infilt t

The final pathologic diagnosis was acute m sternic iral infection ith interst tial pneumonia nd acute myocarditis.

Trichinosis nd myoc rditis

CASE 6 This 19 yea -old Caucasian marine had noted progressi eakness, difficulty in walking, and occasional drenching weat during the month prior t admission while he was bsent ithout lea O admission temperature of 104 F pulse of 130 in regular al us rhythm and igns of trismus, joint tiffness, nd considerable recent eight loss ere noted. The patient held himself in fetal position with contractures of the elbows and knees. Symptoms included questionable meningism no periorbital edema, and large cervical lymph nodes. The hospital course was characterized by fever up to 104 F ith increasing muscular pain fluctua t contractures, nd eosinophilia. Biopsy ex mination of a specimen of muscle revealed Trichina larvae. Laboratory findings included hite blood cou t of 15 900 ith 18 per cent eosinophils creatinine excretion of 1,500 mg for 24 hours total protein of 5.4 Gm per cent with lbumin of 2 9 Gm. A lectrocardiogram showed low oltage R wa es in the limb leads inverted T III prominent precordial S es and slurred QRS complexes on Leads II nd III The patient was treated with hydrocortisone and as maintained for 2 eeks in the hospital on supportiv fluid therapy but he died in respiratory arrest.

At autopsy the myocardium was pink and red soft and pliable with several 3 by 1 mm hemorrhagic treaks in the left entricle.

There was marked interstitial round cell infiltrate of plasma cells, mast cells, lymphocytes, eosinophils, and numerous large swollen-tissue histiocytes resembling epithelioid cells (Fig 5), which cells were bundantly present in the affected striated muscle.

Other autopsy findings included enlarged lungs that eighed 1,380 grams and showed patchy granular consolidation enlarged liver with moderately severe fatty change peptic ulceration of the duodenum superficial lceration of the colon extensiv trichinal infestation of the intercostal and diaphragmatic muscle with scattered inflammatory infiltrate and extensiv fibrin degeneration hyperemia of the brain and brain stem and widespread granulomatous lesions which ere usually adjacent to small blood essels that contained clusters of cerebral histiocytes, *macrophages, round* cells, and some eosinophils other areas showed perivascular cuffing and gliosis.

The final pathologic diagnosis was generalized trichinosis with acute focal myocarditis and meningoencephalomyelitis.

Isolated or idiopathic myocarditis

Idiopathic myocarditis f ch onic fibrous type

CASE 7 The patient was 20-year-old enlisted paratrooper of Spanish descent who had previously had episode of dizziness and loss of ision after carrying hea y bag T eeks later he fainted and had accompanying chest pain There was no history of chest trauma or recent illness H as hospitalized t ice for cardiac evaluation and abnormal electrocardiogram with incomplet right bundle branch block and occasional premature entricular contraction. T wav inversion in Leads V and V was obtained. Results of hest roentgenogram ere normal, and the blood pressure was 130/70 mm Hg Since the patient appeared to be in excellent health it was felt that the changes were congenital or physiologic and he was returned t duty One month later he was found l ing unconscious and was dead on arrival t an Army hospital.

At autopsy the myocardium and endocardium showed 1 to 2 mm. whit areas of fibrosis and myofiber degeneration which extended in broad bands from the pericardial surface. There was scattered interst tial round cell infiltrate predominantly connectiv tissue cells, nd lymphocytes ith rare *plasma cells (Fig 6)*

The final pathologic diagnosis was isolated myocarditis of chronic fibrosing type. A specimen of heart muscle failed t reveal iral growth in culture mediums containing cells of monkey kidney

Idiopathic myoc rd tis of giant cell gra ulomatous type

CASE 8 Eight months prior to admission, this 27-year-old Caucasian male lieutenant had had episodes of malaise and low-back pain. A white cell cou t of 3,000 w h 33 typical lymphocytes was obtained. Three to 4 weeks prior to admission he had had the onset of generalized malaise nd low fever H was admit ed after the development of severe laryngitis with temperature of 100° F blood pressure of 120/80 mm Hg, and pulse of 100.

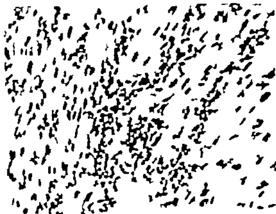


Fig 5 Case 6 acut trichinosis severe acute nd hronic inflammatory response with interstitial edema. (X 240)

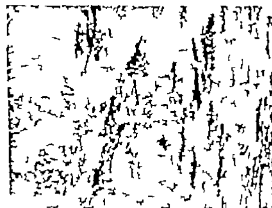


Fig 6 Case 7 idiopathic myocard tis, diffuse bands of fibrous tissue nd areas of hemorrhage (X 60)

Physical examination rev led moder t lymphadenopathy and Grade II/IV soft holosystolic mur mu in the pulmonic area with S_2A equal to S_2P On laboratory examination results of the urinalysis were normal the whit cell cou t was 8 700 ith many typical lymphocytes the hematocrit was 50 Serum glutamic oxalacetic transaminase (SGOT) as 155 nits (normal is 4 t 40 its), cephalin flocculation 4+ alkaline phosphatase as elev ted to 10 Bodansky units. Chest roentgenogram re ealed right upper lobe infiltrat EKG suggested incomplete right bundle branch block with light ST segment depression. The admitting diagnosis was infectious mononucleosis and positiv heterophil titer of 1 to 112 was obtained The patient was treated with penicillin and subsequently discharged from the hospital and scheduled to return t the clinic in 3 eeks. He was discovered dead in his quarters 3 days after discharge.

At topsy the heart, predomina tly the left

ei tricular sept m, showed man small irregula gray tan zones 1 5 cm i diameter

There ere umerou areas of terstitial fibrosis characterized by moderat chronic nflammatory cell i filtrat with increased mbers of connectiv tissu cells (Fig 7) There were numerou foreign bod gia t cells of Langhans t pe on ning ast roid bodies most promine t he interf scu lar septa (Fig 8).

Other topsy findings ere bilater lly enlarged edematous lungs moder t l soft 750 gram spleen revealing sinusoids filled th pla ma ells and t pical mononuclear ell l enlarged liver ith slight periportal ro nd ll infil rat A rare area of lung and h lar ly ph nod ontained giant cells w th asteroid bodie On postmortem bacteri ologic tud bet hemol t ptococ l grew from the blood nd (up A bet h mol t streptococcal



Fig 7 Case 8 gia t cell myocard tis, granulomatous cardiac degeneration with giant cells increased fibrous tissue nd infiltration by lymphocytes. (X 100)



Fig 8 Case 8, giant cell myocarditis Typical cardiac giant cell containing 50 to 100 uclei with asteroid body (see arrow). (X 570.)

immunofluorescence was present in the lung with focal fluorescence of anti 7S globulins around myo ardial fibers which had been fixed in formalin Results of studies with ther special stains, toxicologic immunoelectrophoretic and spectroscopic nalyses of heart lung nd blood were negative.

The final pathologic diagnosi was Giant cell granulomatosis (nonepithelioid) with involvement of heart lu g and lymph node infectious mononucleosis and treptococcal hemorrhagic pneu monitis.

Physical toxic, and metabolic myocarditis

Myoc rditis ssociated with carbon tetrachloride poisoning

CASE 9 This 45-yea -old Caucasia corporal, who had been drinking lcohol on previous evenings, was working in mechanic pit in the presence of large mounts of carbon tetrachloride The following day he developed hills, fever emesis on 4 occasions, epigastric pain and pai and tenderness of the costo ertebral angle On admission the temperature as 97 8° F nd the blood pressure as 180/100 mm. Hg There were scattered rhonchi over the chest Significa t laboratory findings ere white blood cou t of 10,000 ith 74 polymorphonuclear leukocyt blood rea nitrogen (BUN) of 135 mg per cent potassium 7.0 mEq per liter sodium 134 mEq per liter calcium 9 7 mg per cent Urine ex mination showed 2+ protei nd 10 to 12 white blood cells per high-power field An lectrocardiogram revealed high peaked T wa es. The renal f nc tion gradually deteriorated i spite of fluid restric tion high carbohydrate-candy intake and intra enou glucose together w th pressor agents. While being transported by plane from Paris t the United States for renal dialysis, his pulse varied between 52 and 88 with occasional dropped beats and markedly irregular rhythm before his death

At autopsy the heart ppeared normal except for moderat amou t of interstitial edema th pecu-



Fig 9 Case 9 toxic effects of carbon tetrachloride on myocardium with perivascular and interstitial round cell infiltrate in basophilic edema. (X 240.)

Table I. Clinical findings

Case no.	Etiology	Chief complaints	Duration of illness	Clinical cardiac findings	Electrocardiogram	Drug therapy
1	Overwhelming meningococcemia with adrenal cortical hemorrhage	Malaise, lethargy fever	14 hours	Not mentioned	None	None
2	Overwhelming meningococcemia with adrenal cortical hemorrhage	Malaise, backache, pain in limbs	60 hours	Not enlarged, rapid regular heart sounds	None	Sulfisoxazole, oxytetracycline, hydrocortisone, levarterenol
3	Herpes simplex	Seizures	14 days	Normal with febrile tachycardia	None	Diphenylhydantoin, phenobarbital, penicillin
4	Chickenpox	Fever and skin rash	13 days	Normal with febrile tachycardia	None	Oxytetracycline; gentian violet, chlortetracycline
5	Probable viral pneumonia	Pleuritic right chest pain	19 days	Normal with febrile tachycardia	None	Penicillin, chloramphenicol, kanamycin, hydrocortisone, oxygen
6	Trichinosis	Progressive muscle weakness and tenderness of thighs and forearms, night sweats	8-10 weeks	Normal with febrile tachycardia, Grade III systolic murmur at left sternal border	Low voltage R waves in limb leads, inverted T in Lead III, prominent precordial S waves and slurred QRS	Oxytetracycline, hydrocortisone
	Idiopathic myocarditis of diffuse fibrosing type	Dizziness, fainting, chest pain	8-10 weeks	Normal	Incomplete right bundle branch block, occasional VPC's, inverted T V1-V6	None
8	Idiopathic myocarditis of giant cell granulomatous type	Malaise, low fever diagnosed infectious mononucleosis	2-6 months	Grade II/IV systolic murmur in pulmonic area with S_2A equal to S_2P	Incomplete right bundle branch block with slight ST segment depression	Penicillin
9	Toxic myocarditis due to carbon tetrachloride	Chills, fever, emesis, epigastric pain following carbon tetrachloride exposure	6 days	Blood pressure 150/100 mm. Hg, pulse irregular at 52-68 beats per minute with dropped beats	High peaked T waves (K^+ of 7 mg. per cent	Oxytetracycline, ASA, phenacetin, codeine, mannitol, ethacrynic acid, oxygen

lar basophilic staining and perivascular round cell infiltrate with plasma cells, histiocytes, lymphocytes, and a moderate number of polymorphonuclear leukocytes (Fig. 9).

Other autopsy findings included bilaterally enlarged edematous lungs that revealed serous transudate in all alveoli with hyperemia; enlarged pale tan liver with marked central necrosis with hemorrhage and chronic inflammatory cell infiltrate; bilaterally enlarged kidneys that showed extensive cloudy degeneration of tubular cells but no actual necrosis, and occasional hemoglobin casts which were seen in tubules.

The final pathologic diagnosis was Carbon tetra-

Table II. Microscopic findings

Case No.	*Pericardium*	*Coronary vessels*	*Interstitium (edema and type fibrosis)*	*Myofibers*	*Interstitial arterioles and capillaries*	*Cardiac histiocytes*	*Endocardium and valves*	*Gross fibrosis*
1	Normal	Normal	Moderate interstitial edema and infiltrate of lymphocytes and plasma cells	Swollen nuclei	Marked endothelial cell swelling and luminal obliteration by rare fibrin plugs	None	Normal	None
2	Evidence of hemorrhages	Normal	Slight edema, moderate infiltrate of lymphocytes and plasma cells	Rare degeneration, some polymorphonuclear leukocytes	Moderate endothelial swelling	None	Normal	None
3	Normal	Minimal atheromas	Diffuse infiltrate of plasma cells, lymphocytes and some polymorphonuclear leukocytes	Degeneration, variation in staining, lipochrome pigment in cells	Focal areas of vessel degeneration	Marked numbers	Swollen endothelial cells, endocardial infiltrate of lymphocytes and plasma cells	Moderate with marked epicardial scar
4	Evident hemorrhages along coronary vessels, swollen mesothelial cells	Normal	Minimal edema, infiltration with lymphocytes, histiocytes and plasma cells	Cloudy degeneration and fragmentation	Perivascular round cell infiltration	Rare	Normal	None
5	Marked infiltrate of plasma cells, lymphocytes	Minimal atheromas	Slight edema, marked acute and chronic inflammatory infiltrate	Scattered Zenker's degeneration, polymorphonuclear leukocytes, rare eosinophils, and chronic inflammatory cells	Minimal perivascular infiltrate	Moderate	Normal	None
6	Normal	Normal	Marked infiltrate of plasma cells, lymphocytes, some polymorphonuclear leukocytes; numerous swollen tissue histiocytes	Marked degeneration of sarcoplasm	Minimal perivascular infiltrate	Moderate	Normal	None

Table II—*Cont'd*

Case No.	*Pericardium*	*Coronary vessels*	*Interstitium (edema and type of infiltrate)*	*Myofibers*	*Interstitial arterioles and capillaries*	*Cardiac histiocytes*	*Endocardium and valves*	*Gross fibrosis*
7	Normal	Normal	Broad bands of fibrosis, scattered infiltrate of connective tissue cells, lymphocytes, rare plasma cells	Diffuse myofiber degeneration surrounded by histiocytes, fibroblasts, lymphocytes and some polymorphonuclear leukocytes	Normal	Moderate	Normal	Marked bands of fibrous tissue
8	Normal	Normal	Numerous granulomas of fibrous tissue, chronic inflammatory cells and Langhans and foreign body type giant cells	Extensive cloudy swelling and degeneration	Some hyperemic vessels, no perivascular granulomas	Rare	Normal	Marked
9	Normal	Slight atherosclerosis	Marked basophilic edema, lymphocyte and plasma cell infiltrate, marked diapedesis of red blood cells	Moderate cloudy swelling	Marked perivascular inflammatory infiltrate of plasma cells, some polymorphonuclear leukocytes and histiocytes	None	Normal	None

chloride poisoning with acute pulmonary edema and mild interstitial myocarditis.

Discussion

Findings in all 9 cases are summarized in Tables I, II, and III.

The patients in both cases 1 and 2 followed the classic course of fulminating meningococcal infections with death occurring in 12 and 48 hours.

In 110 out of 350 fatal meningococcal infections reported from the Armed Forces Institute of Pathology, death occurred within 24 hours[4]. 76 per cent of these sudden deaths were in soldiers under 25 years of age and over 50 per cent had had prodromal symptoms for less than 12 hours. The presenting features were fever, overwhelming sepsis, pharyngitis, and onset of widespread petechial and purpural lesions after 12 hours of illness. This was followed by peripheral circulatory collapse and death.

Ferguson and Chapman, who reported on 16 autopsied cases of meningococcemia, noted the following cardiac findings in order of predominance: polymorphonuclear infiltration, Zenker's degeneration, mononuclear infiltration, focal necrosis, and thrombosis. Thrombosis is commonly seen in overwhelming meningococcal infections in the lungs, kidneys, adrenals, choroid plexus, brain and rarely in the heart. Similar thrombosis of capillaries and small vessels including the skin was seen in our 2 cases and the heart showed epicardial and endo-

Table III. Gross findings

Case No.	Etiology	Weight of heart (Gm.)	Left ventricular thickness (mm.)	Right ventricular thickness (mm.)	Coronary arteries and aorta	Pericardium	Myocardium	Endocardium	Valves chordae
1	Overwhelming meningococcemia with adrenal cortical hemorrhage	320	12	3	Normal	Normal	Red and uniform	Normal	Normal
2	Overwhelming meningococcemia with adrenal cortical hemorrhage	310	9	—	Normal	Petechial hemorrhages up to 8 mm. diameter	Several small L. ventricular hemorrhages	Small hemorrhages	Normal
3	Herpes simplex	350	15	5	Many focal Atheromatous plaques	Two small fibrous scars 3 mm. in diam. over L. ventricle	Pale with flabby texture	Normal	Normal
4	Chickenpox	290	Normal	Normal	Normal	Subepicardial hemorrhages along left and right circumflex branches	Softened and jaundiced	Normal	Normal
5	Probable viral pneumonia	460	—	—	Normal	25 c.c. of cloudy yellow pericardial fluid	—	Normal	Normal
6	Trichinosis	230	11	3 8	Normal	Normal	Pink and red, soft, pliable with 3 by 1 mm. hemorrhagic streaks	Normal	Normal
7	Idiopathic myocarditis of diffuse fibrosing type	300	15	4	Normal	Normal	Small white streaks 2 by ½ mm.	Small white streaks 2 by ½ mm.	Normal
8	Idiopathic myocarditis of giant cell granulomatous type	300	11	4	Minimal atherosclerosis of aorta	Normal	Small irregular gray-tan masses of up to 1.5 cm.	Normal	Normal
9	Toxic myocarditis due to Carbon tetrachloride	310	9 0	3 0	Coronary arteries normal with scattered aortic plaques	Normal	Normal	Normal	Normal

1

cardial petechiae (Fig. 1). Neither microabscesses or meningococci were demonstrable in the heart. In Moritz and Zamcheck's[8] series of fatal meningococcemias 51 of 81 cases showed myocarditis varying from focal to diffuse interstitial inflammation. Although Saphir felt that meningococcemia rarely produced myocarditis, there is little doubt of severe cardiac involvement in the Waterhouse-Friderichsen syndrome. This is partly on the basis of a small vessel phenomenon which causes both adrenal change and cardiac failure.

The therapy of acute meningococcemia has 2 approaches, (1) antibacterial, with the use of penicillin in preference to sulfonamides, and (2) maintenance of blood pressure and related supportive therapy. Sulfonamides have been implicated as a cause of toxic myocarditis. However one of our cases and a majority in the literature showed myocarditis without sulfonamide therapy. Since the cause of the intractable shock seen in the Waterhouse-Friderichsen syndrome is more likely cardiovascular than adrenal, an attempt should be made at cardiac support.

Case 3 represents the unusual occurrence of myocarditis complicating herpes simplex meningoencephalitis. The characteristic clinical picture, the gross, and microscopic findings in the central nervous system, the fourfold rise in antibody titer and the presence of Cowdry's[3] type A intranuclear inclusions all strongly implicate a herpes simplex etiology.

Most fulminating infections of this type have been reported in newborn infants. Ross and Stevenson, who reported on a mixed series of pediatric and adult cases of herpes simplex meningoencephalitides showed that such cases constituted 19.3 per cent (6/31) of all cases of meningoencephalitis studied during the period by the serologic method. They suggested that when primary infection does occur in the adult, involvement of the central nervous system is more common and more severe than in children. Headache, drowsiness, fever and seizures were common symptoms.

Our patient presented with high fever, meningismus and a severe seizure disorder with focal involvement of the face and at times the extremities. There was an acute condition of the liver, a lung injury, and a bleeding ulcer. Examination of the CNS showed mainly lymphocytes, and there was no increase in erythrocytes—unlike the series of Miller and associates.[15] Presence of coma and convulsions indicated severe neurologic involvement. The patient's intractable shock was the only clue to myocardial involvement. An electrocardiogram was not performed and cardiac glycosides were not administered. Steroids, which may be indicated in certain myocarditides such as rheumatic fever, are usually withheld in an overwhelming infection. Yet the microscopic evidence of myocardial necrosis and sensitivity requires a drug with anti-inflammatory properties. Numerous reports have stressed the contraindications of steroid therapy in viral disease although some reports have shown cortisone interference with viral replication.[22]

Microscopically the myocardium showed an interstitial myocarditis of chronic inflammatory cells which were marked by numerous cardiac histiocytes (Fig. 2). There were areas of increased fibrous tissue and 1 subepicardial scar. The patient with minimal coronary atherosclerosis was 39 years old. He was a heavy drinker and some changes could be due to alcoholic cardiomyopathy.[13] Frozen heart tissue was available but virus was not isolated, and we can only associate the myocarditis with the viral encephalitis.

There are numerous viral causes of myocarditis but very few viruses cause a syndrome of encephalitis with myocarditis. The occurrence of coincidental epidemic encephalitis with myocarditis was noted by Ungar.[1] Herpes simplex does not cause epidemic encephalitis. Saphir[16] felt that since Coxsackie virus so closely resembled encephalo-myocarditis (EMC) virus some relationship with the disease that causes encephalitis in animals might be found. It is thought that this virus rarely affects man, and then not with encephalitis. In reviewing the literature on herpes simplex encephalitis, myocarditis has not been reported as a complication. Manion has, however, observed prior cases in adults of herpes simplex myocarditis.

Hackel, who reported on myocarditis in association with varicella, noted morphologic changes very similar to those in our case no. 4. The severity of the myocarditis

was slight in 4 cases and moderate in 3 cases. Muscle fibers showed occasional necrosis with globular swollen eosinophilic ends. The interstitium showed slight edema and small focal collection of lymphocytes, plasma cells, neutrophil and eosinophils. In our case the most severely involved organs were the heart, liver, lung, kidneys and adrenal glands. The cardiac findings were diffuse interstitial myocarditis.

No etiologic agent was discovered in case 5. Postmortem cultures grew *Klebsiella pneumoniae* presumably from a superinfection. Microscopic examination of the lungs revealed widespread interstitial pneumonia compatible with a viral pathogen. Many cases of myocarditis follow respiratory or other viral illness. In influenza A infections, cardiac complication were more often observed in the convalescent stages. Finland and colleagues reported on 7 cases with initial sign of sepsis progressing in weeks to marked myocardial weakness and dyspnea and were quite successful in culturing the virus. Silber and colleagues found significant rises in influenza antibody titer in 6 out of 23 cases of obscure heart failure associated with viral respiratory symptoms. Other atypical agents associated with pneumonia and myocarditis include psittacosis, pleuropneumonia like organism and salivary gland virus. The most common association of myocarditis and pneumonia is with those of bacterial origin. Saphir and Amromin[19] reported 26 cases of myocarditis in 67 autopsies where bronchopneumonia involved one total lung. The clinical findings, which suggested myocarditis, were the severe cyanosis and dyspnea and the unexpected death. Saphir[2] emphasizes that the virus is rarely cultured from the myocardium in cases with pneumonia and thus the myocarditis is just associated with the pneumonia. He does feel that the pneumonia by reducing oxygen tension aids in establishing viral myocarditis, and this is usually late in the disease. Our patient became intractably dyspneic and cyanotic before death. No electrocardiogram was taken and no cardiac glycosides were administered.

Bornholm's disease or epidemic pleurodynia due to Coxsackie virus, has more often been implicated as the cause of diffuse interstitial myocarditis. The virus has not been implicated in such a destructive interstitial pneumonia as in this case but commonly causes pharyngitis, febrile coryza, bronchitis, and cervical adenitis. It is noteworthy that our patient had pharyngitis that was cleared by penicillin 6 weeks before admission.

Trichinosis presents one of the most interesting forms of myocarditis but one that is often fatal in outcome. The lesion seen in case 6 is similar to that in reported clinical cases and that produced experimentally in the heart of the rabbit. The myocardial lesion usually occurs from 4 to 6 weeks following the infection as in this case. An interstitial myocarditis, with lymphocytes and plasma cell response is seen with scattered areas of fiber necrosis. Eosinophils are common in the lesion but may only reflect the high circulating blood levels. In our case occasional eosinophils were present and the predominant cell in the focal inflammatory areas was a long epithelium like connective tissue cell. This cell may arise from the degenerating myofiber. Edwards and Hood[20] concluded that the cardiac effects of trichinosis were "most likely related to the toxic effects of the larvae, their metabolites, or toxic products produced in the course of the host reaction rather than to the formation of antilarval antibodies and a subsequent antigen-antibody response." In the present case the lesion showed little vascular damage or ischemic change, less marked nuclear change and marked myofiber change only in the area of local inflammation. Here the reaction surrounded the myoplasm and hardly affected the myofiber nuclei. Thus the cellular reaction may indicate a sensitivity to a component of the cell which results in the disintegration of the myofiber but not a lysis of the whole cell or its nuclei. No parasites were seen on numerous sections. Semple and associates,[21] in their report describe foci of up to 1 mm. that showed acute inflammatory reaction with destruction of myofibers, some eosinophils, and no parasites in the heart.

Saphir states that "Isolated or Fiedler's myocarditis is defined as inflammation of the myocardium of unknown origin in the absence of a noteworthy involvement of either the pericardium or endocardium and in the absence of any disease in the course

of which myocarditis is known to occur

Thus only cardiac disease is found at autopsy without antecedent history of cardiopathy. Synonyms for this process are idiopathic, diffuse or interstitial myocarditis. Case 7 is a typical example with an insidious onset in a previously healthy paratrooper who developed substernal pain electrocardiographic manifestations and other signs which were not given sufficient attention. The discovery of viral causes (especially Coxsackie virus) has stimulated research in this area. Serologic studies should be carried out on both acute and convalescent patients. Similarly frozen cardiac tissue from the autopsy will assist in diagnosis. In this case extensive interventricular fibrosis, round cell infiltrate and occasional cardiac histiocytes were seen. Saphir [11] has reviewed the pertinent literature.

House[3] who reported 4 cases of diffuse interstitial myocarditis, noted a pale flabby myocardium. The predominant lesion was a mild to moderate interstitial edema with inflammatory infiltrate that consisted of lymphocytes, plasma cells neutrophils, eosinophils, and macrophages. Cardiac myofibers were usually intact, with rare areas of degeneration fragmentation shrinking and distorted pyknotic nuclei

Granulomatous giant cell myocarditis is a rare but well recognized form of myocardiopathy. Sarcoid has often been implicated in this process and indeed a granulomatous change was found in a single mediastinal node and lung section in case 8. The patient was recovering from infectious mononucleosis, which has been implicated often in diffuse but never in granulomatous myocarditis. Extensive studies for bacterial or hypersensitive etiology were performed and in this case revealed streptococci to be present in the granulomatous lung lesion but not the heart. Kean and Hoekenga[24] reported on 2 cases of granulomatous giant cell myocarditis where an arteriosclerotic etiology was implicated. Our patient had absolutely minimal arteriosclerosis. Microscopic examination showed extensive interventricular fibrosis, probably affecting the conducting system as in case 6 and producing electrocardiograph abnormalities. Giant cells were predominantly of Langhans type with some of myogenic type. Tuberculosis and syphilis have in the past been considered as causative organisms in such a lesion. Rab and colleagues[25] and Cubbay[26] have reported very similar cases recently where supraventricular tachycardias were the major clinical finding with only a temporary response to quinidine or procaine amide. Sarcoid was again considered strongly among other possibilities and in Cubbay's case asteroid bodies were present in the giant cells in some hilar nodes and lung parenchyma—a striking parallel to our case (Fig. 8). Giant cell granulomatous myocarditis remains an enigmatic form of myocardiopathy.

Case 9 illustrates at least 3 possible causes for the inflammatory lesions in the heart. The direct toxic effect of carbon tetrachloride, the effect of electrolyte imbalance and the effect of deranged protein carbohydrate, and fat metabolism. The sequence of microscopic findings parallels Wartman and Hills'[7] description of the changes in toxic myocardiopathy. These authors point out the difficulty in implicating direct effect from that mediated metabolically from other parenchymal organs. Hypoxemia is often implicated especially where findings may include pulmonary damage enzymatic defects from carbon monoxide or cyanide poisoning or capillary damage (as in arsenic poisoning). Drugs such as sulfonamides have been implicated in interstitial myocarditis.[27] Similarly alcohol long thought to mediate a nutritional defect has recently been implicated as a direct cardiotoxin. Patients 3 and 9 both gave a history of alcohol consumption. Evans[11] has described the symptoms of cardiac chest pain breathlessness, unexplained atrial fibrillation and the nonspecific findings of myocarditis in patients with alcoholic cardiomyopathy.

Wuhrmann[27] has categorized the metabolic factors of electrolyte imbalance and dysproteinemia with protean manifestations of the heart. Our patient's death in acute renal failure indicates that the myocardial changes developed suddenly. Wartman and Hill believe that certain poisons cause fairly specific lesions, for instance that phosphorous causes severe fatty degeneration of the myocardium. In our case the microscopic findings of basophilic interstitial edema perivascular round cell fil

trate diffuse interstitial hemorrhage and diapedesis of red blood cells suggest a breakdown of vascular integrity. A direct effect on the myofibers was seen with vacuolization, lipoid degeneration, and nuclear and cytoplasmic changes. The patient died in a state of hyperpotassemia and uremia. While the electrocardiographic changes of hyperpotassemia have been well studied, the microscopic effect of acute hyperpotassemia on the myofiber requires investigation.

These 9 cases represent roughly a 1 per cent autopsy incidence of myocarditis in a military population serving the New York–New Jersey area. In only one case was the diagnosis of myocarditis made before death. Electrocardiograms were performed in only 4 of the 9 cases and glycosides or other cardiac supportive drugs were administered in only one case. Transaminase tests were not done. Yet in the studies of Nydick and associates[4] on active rheumatic carditis, 50 to 88 per cent of cases showed significant elevation. In our cases, the demonstrated necrosis of myofibers indicates a need for enzyme studies.

In each of the cases there was sufficient cardiac disease to be a contributory if not the major cause of death. Much attention is focused on adrenal hemorrhage in cases of meningococcemia but the common occurrence of myocarditis is not emphasized. The common feature in certain of the cases presented is the extreme sensitivity of the cardiac myofiber to systemic illnesses, as seen in cases 1 to 5. The changes seen in trichinosis are also perhaps on the basis of hypersensitivity of the cardiac myofiber to some external agent. In our cases of idiopathic fibrosing and granulomatous myocarditis, cardiac symptoms were prominent and abnormal electrocardiograms were obtained but their significance was not appreciated. In the case of carbon tetrachloride poisoning, arrythmias were present and were thought to result from acute renal failure with hyperkalemia, yet autopsy revealed abundant microscopic cardiac pathology.

No regimen of therapy has been accepted for treating these myocarditides, since treatment is largely symptomatic and focused on the cause if known. Steroids and anti-inflammatory agents, known to be of value in rheumatic carditis, may be applicable to the less common forms of myocarditis. Digitalis therapy is indicated if signs of heart failure appear. Bed rest is mandatory and careful follow-up is required until all signs of cardiopathy have disappeared.

Summary

These 9 cases are examples of the less common and less well-studied causes of cardiac inflammatory disease. Brief summaries have been presented with detailed descriptions of the cardiac lesions. The discussion has examined the etiologic basis for the microscopic changes and has speculated as to the origin of the extreme sensitivity of cardiac tissue to external agents (infectious, metabolic, or perhaps allergic). Suspicion of myocarditis should be the rule in those patients suffering from cardiac failure of unknown etiology or systemic or infectious diseases where myocarditis occurs.

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two leads gave noise figures which were better than the best single lead in all but 3 runs, and better than the second best signal in all runs. (2b) The standard deviation of noise in this selected combination was 18 per cent less than the noise in the best individual lead

Discussion

A complete knowledge of the characteristics of interference in exercise electrocardiograms is essential before noise reduction techniques can be intelligently applied For example time averaging is maximally effective only if the noise is completely random with respect to the ECG signal Slightly correlated noise such as the Markoffian random noise shown to be present in all of the ECG records will reduce the effectiveness of the averaging process. The degree to which the effectiveness of averaging is reduced increases with the time constant of the exponential decay of the autocorrelation function Thus large low frequency artifacts may be difficult to average out because of their nonrandom characteristics and because of the limited number of ECG complexes available from each phase of the submaximal test.

High frequency periodic interference such as hum perturbs the R wave trigger point and results in a partial correlation between the ECG signal and the hum This results in a decrease in the effectiveness of averaging and also a subsequent distortion of the averaged signal [13]

The pilot studies described were examples of the use of the noise measurements and characteristics to make objective evaluations of lead configurations and exercise tests. From the lead configuration evaluation it is apparent that slight variations in the anatomic position of the electrodes may result in a significant change in the signal-to-noise ratio It is natural therefore that these methods could be extended to compare the noise characteristics of any of the conventional or weighted lead systems. The second pilot study gave strong indications that the bicycle ergometer test is consistently less noisy than the Master two-step test. This is not surprising when one considers the relative movements of the electrodes in each of these tests. The relatively stationary position of the upper half of the body during the bicycle test compares with the relatively jerky movements associated with a step test

Spatial averaging of ECG signals either continuously or selectively appears to offer the advantage of "on-line" noise reduction and definitely reduces the possibility that a single bad electrode will ruin an entire record It is interesting to note that because of the lack of correlation of the noise in each channel it is possible to obtain an equally weighted average that may be better than the best individual lead This spatial averaging is an inherent characteristic of any weighted lead system However this averaging does not guarantee a signal less noisy than that from the best single lead It must be remembered that in advance we do not know which lead is going to be the best. All that has been shown is that there is a high probability that the weighted signals will be a distinct improvement over the average individual lead

Summary

Signal processing techniques were developed to analyze hum and noise the two main factors influencing the quality of exercise electrocardiograms. Hum was accurately evaluated by Fourier analysis methods, and the noise characteristics by appropriate sampling procedures and autocorrelation analysis.

In a sample study of 41 typical exercise ECG records, the average hum over a 3-minute record was 34 μv peak to peak with a minimum of 4 μv peak to peak and a maximum of 340 μv peak to peak Noise was found to closely approximate Markoffian random noise plus periodic components closely correlated to both the periodicity of the exercise test and of respiration. The total noise varied from a root mean square value of 60 μv to a maximum of 915 μv The periodic noise power averaged 8 per cent of the total noise power with a minimum of 1 per cent to a maximum of 30 per cent of the total power

Pilot studies were made to determine differences in the noise content due to slight variations in the anatomic position

of the electrodes, and due to different stress tests. Significant and consistent variations were seen in noise content of electrodes whose position varied slightly. Similarly it was determined that the average standard deviation of the noise in the Master two-step test was about 50 per cent higher than that from a bicycle ergometer test.

An improvement in the average signal-to-noise ratio was found by means of spatial averaging, i.e., linear weighting of the signals from electrodes located very close together anatomically. This real-time averaging also reduced the statistical chance that a single bad electrode would ruin an entire record. Also of considerable interest are the encouraging results when multiple redundancy of leads was employed. Here, instead of continuously averaging all 3 signals from the closely spaced electrodes, all signals were continuously monitored and the best combination of 2 leads was selected. This selected combination gave noise figures that were better than the best single lead in all but 3 out of 19 test runs.

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Early premature ventricular beats, repetitive ventricular response, and ventricular fibrillation

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Interruption of the T wave by the succeeding premature QRS complex is a phenomenon of considerable physiologic interest and clinical importance.[1-4] It may provide information concerning changes in the refractory period and the vulnerable phase of the heart, and it also has important therapeutic and preventive implications. Three cases are reported in which spontaneous premature ventricular beats interrupting T waves heralded the onset of fatal ventricular fibrillation (2 cases) and repetitive ventricular responses (1 case).

Case reports

Case 1. A 56-year-old woman was hospitalized about 12 hours after the sudden onset of severe precordial pain that radiated to the left arm. Physical examination revealed an anxious patient complaining of chest pain. Brachial arterial pressure was 150/80 mm. Hg. While she was still in the emergency room, an electrocardiogram was taken which showed early ventricular premature beats and a recent anteroseptal infarction (Fig. 1). Ventricular fibrillation ensued while Lead V was being registered. Closed-chest massage was unsuccessful.

Case 2. A 60-year-old man suffering from arterial hypertension was examined because of epigastric distress which had been present for some hours, and which was accompanied by cold sweat and an episode of syncope. Physical examination revealed an obese sweaty man in no distress. Brachial arterial pressure was 140/80 mm. Hg. Auscultation of the heart revealed several premature beats. The electrocardiogram revealed premature atrial and early ventricular ectopic beats, and an acute posterior myocardial infarction (Fig. 2). While Lead V was being recorded fatal ventricular fibrillation ensued.

Case 3. A 54-year-old woman was hospitalized on April 24, 1966, with a history of dizziness and dyspnea on effort of several weeks' duration. She had been told 8 years previously that she had "heart disease," but she had otherwise led a normal life. An electrocardiogram that had been recorded 4 days before admission revealed sinus rhythm and a pattern of left ventricular hypertrophy (Fig. 3, A). Physical examination showed an obese, very apprehensive woman. Brachial arterial pressure was 170/110 mm. Hg. There was a rapid, irregular heart beat and a soft apical systolic murmur. The electrocardiogram showed a pattern of left ventricular hypertrophy and isolated early premature ventricular beats of multiform shape (Fig. 3, B). There was a modest elevation of the erythrocyte sedimentation rate and of blood urea. Other laboratory examinations, including serum electrolytes, were normal. Short runs of ventricular multiform tachycardia appeared on May 10, 1966, despite antibiotics and lenalme (Fig. 3, C). Quinidine, 0.20 Gm. orally every 8 hours for a total dose of 1.80 Gm., was then given to the patient from May 21 to May 23. On May 24 numerous bouts of ventricular multiform tachycardia were recorded (Figs. 3, D and 4). Quinidine was discontinued and diphenylhydantoin, 100 mg. three times daily, was administered orally from May 24 until the patient was discharged 1 month later. Ventricular ectopic beats gradually disappeared and the patient was discharged much improved with a tentative diagnosis of subacute myocarditis of unknown origin.

Discussion

T wave interruption is rarely seen with abnormally short coupling intervals in the

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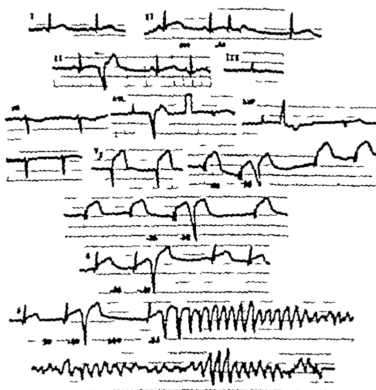


Fig. 1. There is sinus arrhythmia [illegible] ith the heart [illegible] t [illegible] arying from 83 t[illegible] 54 per minute [illegible] the Q-T interval is 0.42 second in Lead V. The first extrasystolic beat [illegible] hich signifies the onset of [illegible] entricular arrhythmia has the same [illegible] hape as the t[illegible] preceding premature beats. Then follow [illegible] short period about 3 seconds, of ventricular flutter (or tachycardia) [illegible] t [illegible] rate of 200 to 300 per minute [illegible] continuing into [illegible] entricular fibrillation. The fourth and the fifth and also the last t[illegible] strips of the record are continuous.

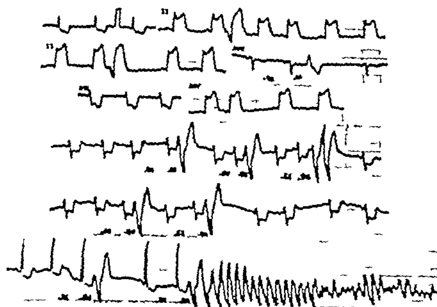


Fig. [illegible] Sinus arrhythmia [illegible] th the heart rat[illegible] arying from 63 to 81 per minute. The Q-T interval is 0.42 second in Lead V. Ectopic [illegible] entricular beats are monomorph. Ventricular fibrillation follow[illegible] short run of [illegible] ventricular flutter (or tachycardia) [illegible] t [illegible] rate of 188 to 300 per minute [illegible] nd lasts [illegible] bout 3 seconds. The fourth and the fifth [illegible] trips are continuous.

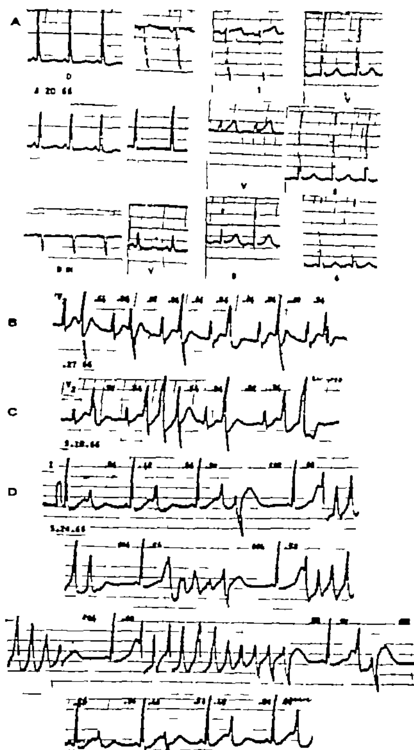


Fig. 3. *A*, There is sinus rhythm at a rate of 94 per minute and a pattern of left ventricular hypertrophy. A U wave [illegible] is probably superimposed on the T wave. The Q-T interval in Lead V is 0.38 second. *B*, Multiform isolated ventricular beats occur before the completion of the T wave. *C*, Premature ventricular beats are now coupled and in short runs. *D*, Four continuous strips showing ventricular premature beats which occur [illegible] first isolated, then coupled, and then in runs of ventricular multiform tachycardia. The last strip shows return to ventricular bigeminy. Note the varying length of coupling intervals and alterations in the shape of the T wave.



Fig. 4. Alterations in the shape of the T [illegible] are shown in greater detail (paper speed of 50 mm. per second). There is probably summation of U on the T [illegible]. The third strip shows the change of the T [illegible] then [illegible] then returns.

presence of a normal Q-T duration or more commonly with coupling intervals in the usual range in the presence of a prolonged Q-T. It has been stressed that distinction between the two groups of cases has great practical importance since the use of quinidine or procainamide appears to be indicated in the former group but dangerous in the latter one. Case 3 points out that there may be some difficulties in selecting cases. In this patient, the Q-T interval was at the upper limit* (Fig. 3,A) and coupling intervals were at first short (Fig. 3,B, C). Tentative therapy with small oral doses of quinidine was therefore initiated. Four days later lengthening of both the coupling intervals and Q-T duration was manifest and because of repetitive ventricular responses (Fig. 3,D) quinidine was discontinued. Diphenylhydantoin was then given and was successful in abolishing paroxysmal ventricular tachycardia and ventricular extrasystoles in this patient.

In Cases 1 and 2, T wave interruption initiating ventricular fibrillation occurred on the downslope of the T wave (Figs. 1 and 2) whereas in Case 3 ventricular repetitive responses were initiated on the summit of a well-developed U wave[7] (Figs. 3,D and 4). The longer refractory period in the latter case might be responsible for this finding.

Coupling intervals were plotted against the preceding R-R intervals in Case 3. Observed was a linear increase in the shortest coupling intervals with decreasing heart rate (Fig. 5). This was most likely related to the change in the refractory period at different heart rates.[16] Moreover the scattering of repetitive ventricular responses suggested that the vulnerable phase was located at a certain distance from the boundary of the absolute refractory period although casual scattering could not be ruled out.

Many experimental[13] and clinical[3-15] data point out that, when there is some change in the excitability of the heart, extrinsic impulses having an intensity only a few times greater than threshold can determine ventricular responses and fibrillation if applied during the vulnerable phase. There is therefore no difficulty in admitting that an ectopic stimulus originating in the heart and therefore of threshold energy value might determine those arrhythmias when occurring at the expected vulnerable period. Once induced the chaotic ventricular arrhythmia will perpetuate itself if the mean refractory period is sufficiently brief or if the conduction velocity of the heart is sufficiently slow.

*The difficulties in determining the actual duration of an interval in clinical electrocardiography can be summarized thus: (a) Measurements cannot be made closer than 0.04-0.05 second. (In the present paper records are made with [illegible] electrocardiograph [illegible] paper speed of 25 or 50 mm. per second and measurements no closer than 0.02 second.) (b) Simultaneously recorded leads [illegible] the electric course of the phenomena are rarely available. (c) Different observers may assign widely divergent values to an interval of the same tracing when difficulties in the definition of the points to be used for measurements are given.

Summary

Three cases are reported in which early premature ventricular beats were followed



Fig 5 Relationship of the coupling intervals of 316 ventricular extrasystoles interrupting T waves (QF on ordinate) to the preceding Q-Q intervals (on abscissa) occurring in Case 3 from April 27 to M 31 Solid circles indicate three measurement half circles indicate two and open circles indicate one. Triangles indicate premature beats of Cases 1 and 2 *R* signifies repetitive ventricular responses (runs of three ectopic beats or more) in Case 3 and *F* denotes ventricular fibrillation in Cases 1 and 2. The dotted curve indicates the average Q-T interval

by ventricular fibrillation (2 cases) and repetitive ventricular responses (1 case) The relationship of these findings to the vulnerable phase is discussed

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Tryptophan and serotonin levels in patients with or susceptible to, African cardiomyopathy

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It has recently been shown that a diet containing a high proportion of ground maize (corn—*Zea mays*) which resembles that of many Africans of South Africa produces a cardiomyopathy in rats after a prolonged period of time. The histologic appearance of the experimentally diseased heart closely resembled that of the human cardiomyopathy to which this population is peculiarly susceptible, termed African cardiomyopathy in previous reports from this laboratory.[1-4] A feature of the diet was its low content of tryptophan and plasma tryptophan levels in the rats were shown to correlate inversely with the severity of the experimental lesion. Spatz[5] has more recently shown that in guinea pigs a tryptophan-deficient synthetic diet produces acutely a cardiomyopathy that is prevented by the simultaneous administration of serotonin for which tryptophan is the essential dietary precursor.

Before the relevance of tryptophan to the human lesion is proved it is necessary to demonstrate in human patients (1) a deficiency of tryptophan at least during the stage of pathogenesis of the cardiac lesion and (2) prevention of the lesion during the stage of pathogenesis by tryptophan supplementation. The present report is of investigations concerning the first point. The plasma tryptophan and serotonin levels of various groups of patients were investigated.

Methods and patients

Plasma tryptophan was estimated in the fasting patient by the method of Duggan and Udenfriend modified as previously described.

Serum for estimation of serotonin was treated according to Davis, the estimation was by the method of Weissbach.

All patients were African investigated either on an outpatient basis or immediately after admission to the wards of the teaching hospital. All samples of blood were taken in the morning between 8 and 10 A.M., the patients having had nothing to eat since 6 P.M. the previous day.

The groups of patients were as follows: *Group 1*. Patients diagnosed as having African cardiomyopathy, all being in congestive cardiac failure for the first time. *Group 2*. Pellagrins. *Group 3*. Patients with congestive cardiac failure due to rheumatic valve disease or hypertension. *Group 4*. Patients with disorders not considered to have any specific reason for abnormality of tryptophan or serotonin levels, e.g.

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osteoarthritis, peripheral neuritis, epilepsy. The patients were similar in age range to those of groups 1-3 and are considered as the controls for Groups 1-3, since they represent the same population in social and economic circumstances attending the same hospital as that from which these other groups were drawn. *Group 5*: Patients with single 24-week pregnancies. *Group 6*: Patients with single 40-week pregnancies, in early labor. *Group 7*: Patients with twin pregnancies of between 32 and 40 weeks of duration, not in labor. *Group 8*: Mothers who had delivered 4 weeks previously after single pregnancies. All were lactating. *Group 9*: Mothers who had delivered 4 weeks previously after twin pregnancies. All were lactating. *Group 10*: Mothers who had delivered single babies 1 to 3 years previously, not lactating. These are taken as controls for Groups 5-9 rather than the females of Groups 1-4 because the obstetrical patients were thought to be drawn from a slightly different population than the general medical patient.

Results

The findings are shown in Table I. Tryptophan and serotonin levels are from the same patients, but not all patients underwent both investigations.

Discussion

At the time a patient presents with heart failure due to African cardiomyopathy, his heart is likely to be so affected by fibrosis that his recent tryptophan intake, if tryptophan is related in any way to the pathogenesis of the condition, may well be irrelevant.

Indeed, it is not uncommon to elicit a history of a reasonable diet over the last years prior to the onset of congestive failure with a history of high intake of ground maize previous to that. The finding of normal levels of tryptophan and serotonin in such established cases is, therefore, not unexpected, even if these are related to pathogenesis.

The group from which evidence should be forthcoming of a poor tryptophan status is that group shown particularly to be at risk from precipitating factors—pregnancy and the postpartum.[4,5] Evidence is forthcoming on this point from the present study. The tryptophan deficiency, moreover, appears to be most severe in patients who have had twin pregnancies, which patients are even more susceptible to the disease.[5] The normality of the patients in early labor as regards tryptophan is in contrast to those in earlier pregnancy and in the early post partum and may reflect the effects of labor on protein metabolism. Nevertheless, they still show a marked decrease in serum serotonin levels. The deficiencies continue in the post partum, but a year after delivery both values have returned to normal. This again correlates with clinical experience in that the risk of manifest heart failure does not appear to be greater in the female at this time than at any other time unassociated with pregnancy.

The report of a cardiomyopathy indistinguishable from African cardiomyopathy occurring in Colombia[1] is of interest in view of dietary habits in that country. Observations from there in regard to the clinical and biochemical effects of pregnancy parallel to the present ones would be desirable. Observations on twin pregnant mothers are currently under way at this laboratory.

Values of plasma tryptophan in the control (noncardiac) patients and in those with congestive cardiac failure due to causes other than African cardiomyopathy are slightly lower than the normal value (10 µg per milliliter) reported for the method and may reflect the general protein malnutrition of the local African hospital patient population, manifested, for example, by the incidence of kwashiorkor in its infants.

The deficiency of serotonin in the blood of the patients at risk assumes importance in view of the experiments of Spatz previously quoted. The mechanism by which the cardiac lesion is produced is still obscure, despite her demonstration of changes in phosphorylase activity in the heart.

The tryptophan levels in these patients were as low as in pellagrins, but a difference is seen in the serum serotonin values. Nevertheless, the heart in pellagrins is not normal. Hudson[1] gives references to authors reporting electrocardiographic changes in pellagrins which were reversed by nicotinic acid, and Wyndham

Table I

Group	*Sex*	*Number in group*	*Plasma tryptophan level* ($\mu g/ml \pm S.E.$)	*p Value*	*Number in group*	*Serum serotonin level* ($\mu g/ml \pm S.E.$)	*p Value*
1 African cardiomyopathy	M	15	8 78 ± 83		6	62 ± 26	
	F	18	7 57 ± 37		15	48 ± 12	
2. Pellagrins	M	7	5 7 ± 59	< 05	2	31 ± 04	
	F	9	7 08 ± 55		6	30 ± 12	
3 Congestive cardiac failure	M	17	8 45 ± 59		15	24 ± 06	
	F	16	8 63 ± 92		13	44 ± 10	
4 Noncardiac patients	M	17	8 18 ± 74		15	28 ± 12	
	F	15	7 46 ± 94		11	46 ± 12	
5 Single pregnancy 24 weeks	F	15	6 63 ± 33	< 001	0		
6. Single pregnancy 40 weeks	F	17	7 86 ± 35		17	06 ± 01	< 001
7 Twin pregnancy 32-40 weeks, not in labor	F	16	5 64 ± 75	< 01	6	09 ± 04	< 1
8 Mothers, 4 weeks after delivery single babies	F	26	6 64 ± 44	< 01	26	51 ± 06	
9 Mothers, 4 weeks after delivery twin babies 1 month old	F	6	6 34 ± 1 03	< 02	4	16 ± 05	
10 Mothers, 1 2 years after delivery single babies	F	15	8 91 ± 48		14	30 ± 07	

Value (t test) Groups 1 3 compared with Group 4 of same sex based on combined variance Groups 5 compared with Group 10
Comparison of Group 1 with Group 4 females shows no significance of difference of the means for tryptophan or serotonin

and associates,[12] in an important paper have demonstrated the similarity of the pattern of cardiovascular response to work in pellagrins to that in hospitalized patients suffering from African cardiomyopathy In some aspects the pellagrins were actually more abnormal than the cardiac patients—their heart rates and stroke volumes diverged farther from the normal curve with increasing oxygen consumption and maximum oxygen consumption was less.

Summary

Lowered levels of plasma tryptophan are reported in patients with pellagra, in those who were pregnant and in those in the post partum period. Low values of serum serotonin were observed during pregnancy The relevance to the pathogenesis of African (idiopathic) cardiomyopathy is discussed

The patients were studied by permission of the Medical Superintendent, King Edward VIII Hospital, Durban South Africa.

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Experimental and laboratory reports

Histochemical and electron microscopic study of heart muscle after beta adrenergic blockade

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The pharmacophysiologic properties of and the clinical responses to the newer beta adrenergic receptor blocking compounds have been studied intensively during the past few years. However, the structural and biochemical effects of these compounds on heart muscle have received little attention. The present study was carried out in a series of mice to define the histologic and metabolic effects of beta adrenergic blockade with propranolol† on the myocardium.

Material and methods

Thirty-six adult Swiss white mice with an average body weight of 20 grams were divided equally into three groups. One group received 0.1 mg., a second group 0.01 mg., and a third group 0.005 mg. of propranolol daily for 3 weeks by intraperitoneal injection. One untreated animal in each litter served as control. All the animals survived and were killed at the end of the 3-week period. The hearts were removed and representative tissue blocks were taken for electron microscopy, with the remaining tissue being frozen for cryostat sectioning. The control and experimental tissues were processed simultaneously.

The following techniques were employed: conventional staining with hematoxylin and eosin, PAS reaction for carbohydrate, caffeine-benzpyrene for fluorescence microscopy of lipids, and staining reactions for cytochrome oxidase, succinic, lactic, beta hydroxybutyric, and alpha-glycerophosphate dehydrogenases, calcium- and magnesium-activated adenosinetriphosphatase, acid phosphatase, phosphorylase, and 5-nucleotidase.

Electron microscopic studies were carried out on multiple samples from each of the four cardiac chambers cut into 0.5-mm. cubes. The tissues were fixed for 2 hours in phosphate-buffered osmium tetroxide, dehydrated in a graded series of alcohols, and embedded in a Maraglas-Cardolite mixture. Sections were made with an LKB Ultratome and examined under a Siemens electron microscope after lead citrate staining.

Results

Intake of food and general condition of the mice. Intake of food and ingestion of

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water were maintained throughout the 3-week experimental period in all mice. There was no loss of weight, and none of the animals appeared to suffer adversely from the drug. All of the animals survived.

Histologic and histochemical observations. Except for distention of the small intramyocardial blood vessels, the hearts of the experimental animals appeared to be normal in sections with stained hematoxylin and eosin. The most striking histochemical changes consisted of patchy areas of myolysis (Figs. 1 and 2) with zonal fragmentation of the myofibers (Fig. 3). These lesions were distributed throughout all four cardiac chambers but tended to occur most frequently in subendocardial and perivascular areas. In the mice that received 0.1 mg. of propranolol daily, more advanced confluent lesions were often observed, particularly in the interventricular septum (Fig. 4).

In the mice that received 0.005 mg. or 0.01 mg. of propranolol daily, focal myolytic lesions in various stages of development could be seen in the same section. The less severe myolytic lesions displayed increased succinic and lactic dehydrogenase activity, whereas in the more advanced lesions these enzymes were absent or diminished. This imparted a characteristic moth-eaten appearance to some sections because of the fact that some mitochondria remained inactivated and unstained by the succinic and lactic dehydrogenase preparation, whereas other mitochondria were enlarged and darkly stained (Fig. 1). Fragmentation of the myofibers was well demonstrated in longitudinal sections by marked diminution or complete absence of succinic dehydrogenase activity adjacent to intercalated disks (Fig. 3). Beta-hydroxybutyric dehydrogenase activity was generally increased compared to the control, whereas relatively little change in cytochrome oxidase and alpha-glycerophosphate dehydrogenase activity was observed.

No differences in mitochondrial and myofibrillar adenosinetriphosphatase activity was noted between experimental and control animals. However, ATPase activity was greatly increased in the endothelium of small blood vessels and capillaries of the propranolol-treated animals, as compared to control (Fig. 5). The periodic acid Schiff reaction indicated that the myolytic lesions were free of glycogen, whereas unaffected areas of myocardium displayed normal PAS reaction. The accumulation of lipid drops occurred only rarely.

There was a good correlation between 5-nucleotidase activity and the degree of myocardial damage. In control animals 5-nucleotidase was mainly demonstrated in the endocardium, with only a weakly positive reaction in myocardial fibers. The focal myolytic lesions displayed a strongly positive 5-nucleotidase reaction. The most intense reaction for 5-nucleotidase occurred in the advanced confluent myolytic lesions of the mice that received 0.1 mg. of propranolol daily (Fig. 4). Similar changes of increasing reaction with increasing damage were observed for acid phosphatase activity.

Phosphorylase activity was considerably diminished in heart muscle of experimental animals, as compared to control (Fig. 6). This was particularly true for the subendocardium and the papillary muscles.

Electron microscopic observations. The mitochondria appeared to be swollen and vesicular with disruption of the cristae (Fig. 7). Many of the degenerating mitochondria contained ovoid inclusions, and some were shrunken and fragmented (Fig. 7). Between the altered mitochondria large dense bodies (myelin figures) with concentric, electron-dense lamellae were to be seen (Fig. 7). The myofibrils were greatly stretched with lengthening of the I bands (Fig. 8). Glycogen granules were markedly reduced or absent. The sarcoplasmic reticulum was essentially normal.

Discussion

Daily administration of 0.005 mg. or 0.01 mg. of propranolol in mice for 3 weeks was associated with the development of focal myolytic lesions in the myocardium which became more extensive and confluent when the dosage was increased to 0.1 mg. daily. Succinic and lactic dehydrogenase activity was increased in the large clumped mitochondria of the early myolytic lesion. However, as the lesion became more advanced, succinic and lactic dehydrogenase activity was diminished or

(Text continued on page 350)

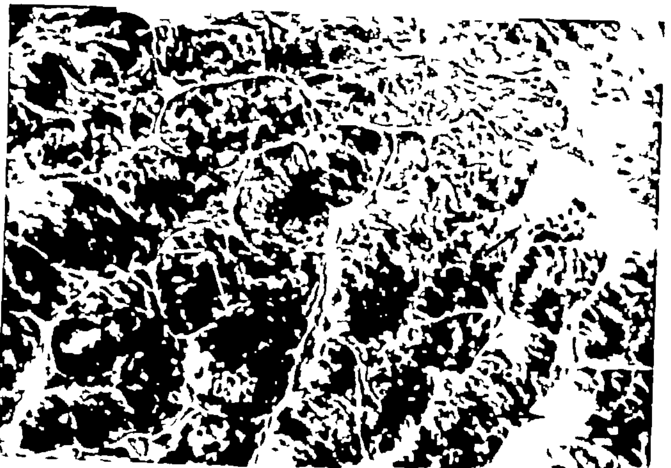


Fig. 1 Cross section of mouse myocardium 3 weeks after propranolol, 0.005 mg. daily (lactic dehydrogenase preparation). There is partial to complete loss of mitochondria in some of the affected fibers (*black arrows*). Where enlarged, dark mitochondria heavily stained by tetrazolium are seen in other fibers (*white arrows*). Magnification ×780.

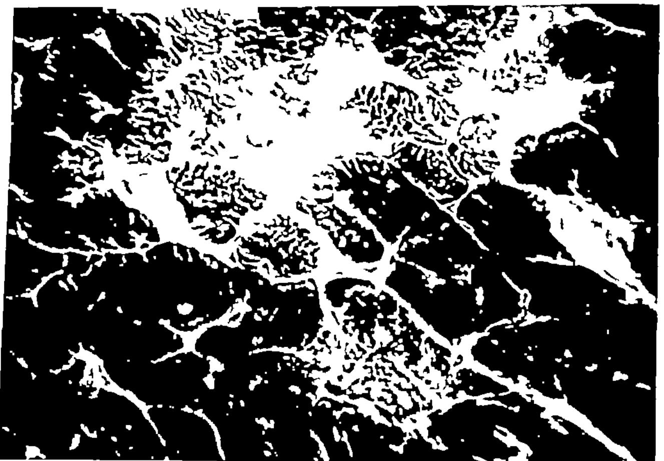


Fig. 2. Mouse myocardium (subendocardial region of left ventricle) 3 weeks after propranolol 0.01 mg daily (succinic dehydrogenase preparation). Note the markedly decreased enzymatic activity in the affected myofibers. Magnification ×500.



Fig. 3 Longitudinal section of mouse myocardium 3 weeks after propranolol, 0.01 mg daily (succinic dehydrogenase preparation). There is fragmentation of the myofibers with decreased enzymatic activity in the mitochondria of the affected fibers. Clumping of the mitochondria (*arrows*) is also present. Magnification ×500.

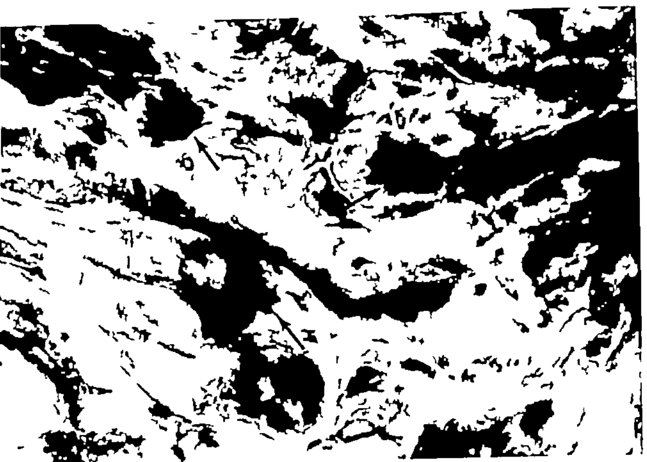


Fig. 4. Mouse myocardium (interventricular septum) 3 weeks after propranolol, 0.1 mg. daily (5'-nucleotidase preparation). There is strong 5'-nucleotidase activity in the degenerating myocardial fibers (*arrows*). Magnification ×500.



Fig. 5. Mouse myocardium 3 weeks after propranolol, 0.01 mg. daily (adenosinetriphosphat preparation) \ ↑ the dilated perifibrillar blood vessels. Magnification X500.

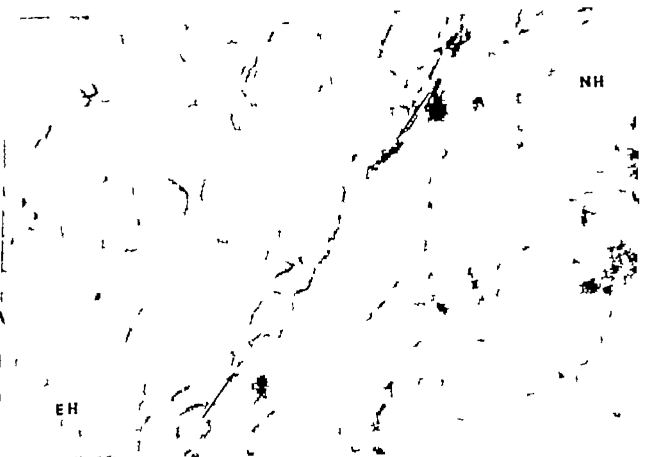


Fig. 6 Mouse myocardium 3 weeks after propranolol. Myocardial phosphorylase activity of control mouse (*NH*) and a propranolol-treated mouse (*EH*). The arrows mark the contact between the epicardial surfaces of the two hearts. Phosphorylase activity is markedly depressed in the propranolol treated mouse. Magnification ×500

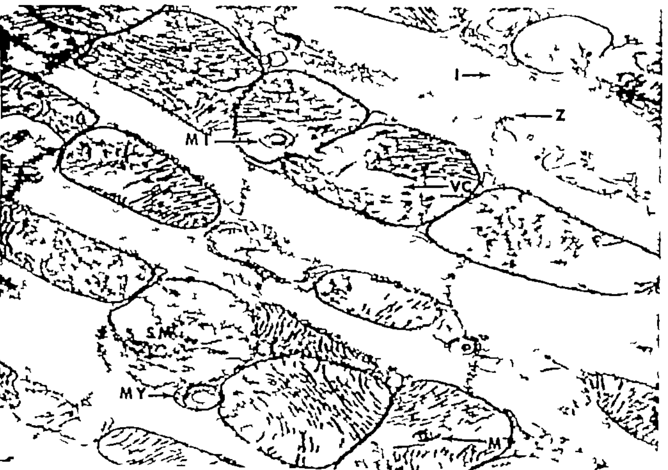


Fig. 7. Electron photomicrograph of right atrium of mouse 3 weeks after propranolol 0.01 mg daily. The mitochondria are in various stages of degeneration with swelling (SM) and vesiculation (VC) of the cristae. Mitochondrial inclusions are in evidence (MT) and myelin figure (MY) found between altered mitochondria. The sarcomeres exhibit increased osmophilia at the Z lines (Z) and widening of the I band (I). The elements of the endoplasmic reticulum are essentially normal. Magnification ×28,000.



Fig. 6. Electron photomicrograph of mouse right ventricle 3 weeks after propranolol 0.01 mg. daily. There is degeneration of the mitochondria with vesiculation (VC) and fragmentation (FM) of the cristae. Note also the mitochondrial inclusions (MI) and the loss of glycogen granules. Magnification ×28,000.

absent As the lesion became more severe 5 nucleotidase and acid phosphatase activity increased Electron microscopic studies showed degeneration of mitochondria in the affected myofibers and an almost universal increase in the length of the I bands and sarcomeres

The mechanism whereby propranolol produced the myocardial lesions described is unknown Similar lesions are well known to occur with h p xi Although propranolol decreases stroke output and coronary blood flow t lso decreases heart work, myocardial contractility and myocardial oxygen requirements [3,4] However in previous studies in dogs it was found that beta adrenergic blockade with propranolol resulted in marked increase in left atrial pressure as well as an increase in heart size Thus the possible metabolic advantage associated with decreased myocardial oxygen requirements occurs in the presence of a mechanical disadvantage e increased heart size and left atrial pressure In the present study lengthening of the I bands suggested that the hearts of the propranolol treated animals were in a distended state. Although the rate of development of tension may decrease after beta-adrenergic blockade the total tension developed by the myocardium must increase since heart size increases and intraventricular pressure remains unchanged [11] The combination of decreased coronary blood flow and increased myocardial tension may have been sufficient to result in hypoxia in spite of the decreased myocardial oxygen requirements.

A second possibility which might explain the myocardial lesions associated with the administration of propranolol is that the compound may be directly toxic to the myocardium.

Previously we suggested on the basis of hemodynamic data that the administration of propranolol may be hazardous in patients who have dilated hearts, with or without overt signs of congestive heart failure.[11] The present studies lend morphologic and biochemical support to this suggestion

Summary

The administration of propranolol a beta-adrenergic receptor antagonist, in mice resulted in the development of myolytic lesions in the myocardium The lesions were focal in mice that received 0.005 mg or 0.01 mg of propranolol daily for 3 weeks whereas more advanced confluent lesions were found in mice that received 0.1 mg of propranolol daily for 3 weeks

The mechanism whereby propranolol produced the myolytic lesions is unknown Decreased coronary blood flow or a direct toxic effect on the myocardium seem to be the most likely possibilities. Inasmuch as beta-adrenergic blockade is being advocated in the treatment of patients with a wide variety of cardiovascular diseases more study of the effects of beta-adrenergic antagonists on heart muscle is needed

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On electrocardiographic-autopsy correlations in left ventricular hypertrophy A simple postmortem index of hypertrophy proposed

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There have been many studies of the correlations between the diagnoses of left ventricular hypertrophy (LVH) on electrocardiographic (ECG) and postmortem (PM) grounds.[27] Various factors, not generally stressed affecting the ECG and PM diagnostic criteria of LVH may have seriously disturbed many of the findings reported in these studies. Taking first the ECG criteria one may group them as follows (1) increase in QRS amplitudes in various leads, taken either singly or in combination (2) left axis deviation (LAD) (3) prolongation of the ventricular activation time (VAT) and (4) ST T changes. Although the usefulness of the ECG in the diagnosis of LVH seems established it is generally agreed that false positives and false negatives tend to be common [14-23,24-26] Low specificity giving rise to false positives, can only be raised by producing low sensitivity giving rise to false negatives, and vice versa.[1,27,28] Most of the comments in this communication relating to ECG criteria apply to increased QRS amplitudes—the so-called *voltage criteria* However before dealing with these a few comments will be made with respect to the other three criteria.

Left axis deviation Whether one speaks of electrical axis in the sense that Einthoven[1] used it, the mean electrical axis,[40-44] or the orientation of the frontal plane vectorcardiographic loop[45,47] there is evidence of a weak, yet significant correlation between LAD and LVH.[22] Accurate determination of the electrical axis requires multichannel recorders with increased paper speeds or better still a vectorcardiographic display LAD is usually regarded as a minor criterion of LVH[23,24] However a tendency to LAD coincides with a tendency for the heart vector to lie in the transverse plane which can increase QRS amplitudes in standard chest leads so that there is a relationship between some of the voltage criteria and LAD[21,24] Nevertheless the inclusion of LAD as a criterion may improve the ECG diagnosis of LVH with the use of voltage criteria[31]

Ventricular activation time Criteria relating to the VAT derive from the concept

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of intrinsicoid deflection The term VAT first used by Sokolow and Lyon [22] refers to the time interval between the onset of the QRS complex and the onset of the steep downslope in precordial leads This down slope was called the intrinsicoid deflection by Wilson and associates who considered it to arise from the so-called *intrinsic deflection* seen on the surface of the heart brought to fame by Lewis and associates [33 34] Unfortunately as pointed out by Dower [35] intrinsic deflection has been employed differently by various authors and even by the same author on different occasions it has also been applied incorrectly to intrinsicoid deflection seen in precordial leads.[37] If such deflections are considered capable of indicating activation of the immediately underlying myocardium which is implied when they are termed intrinsicoid the concept that body-surface potentials can be considered to arise from a single heart vector or dipole is untenable The view of vectorcardiographers that a single cardiac dipole seems to be at least a fair first approximation of a diffuse cardiac generator is supported by the observation that signals resembling conventional precordial lead signals can be obtained from lead resolvers which use as inputs the x y and z orthogonal leads.[46-48] Still significant nondipolar component are known to be present [49] Since electrocardiographers have tended to think more vectorcardiographically [41 42 43] there has developed a tendency to demote the intrinsicoid deflection—a process which has possibly been accelerated by its ambiguity Perhaps it is not surprising that the questionable nature of the intrinsicoid deflection should have prompted the dismissal of the VAT as lacking any sound physical basis [49] Indeed the issue appeared closed when Sano and associates[55] concluded from microelectrode studies of the turtle's heart that no relationship existed between the intrinsic deflection and local activation incontrovertibly indicated by the upstroke of the transmembrane potential curve Curiously this was not the last word and as so often happens in science the careful studies of early workers have been questioned only to be validated by later workers.

The findings of Lewis and colleagues,[34] based on unipolar electrodes and the intrinsic deflection have been supported by modern studies of ventricular activation employing differential electrodes. [57] Also the time coincidence between activations, as indicated by the two methods, has been demonstrated Further microelectrode studies employing a similar though more refined technique on guinea pig heart demonstrated that an accurate coincidence does exist between the intrinsic deflection and the upstroke of the transmembrane potential curve However proof of the existence of a truly intrinsic deflection on the surface of the ventricles does not necessarily imply the existence of an appreciable intrinsicoid deflection over the precordium In any case it is questionable whether conventional electrocardiographs display QRS events with sufficient clarity for the onset of an intrinsicoid deflection if present to be recognized [70] Nevertheless, whatever the theoretical and practical considerations involved the VAT has proved to have some value in the diagnosis of LVH high specificity but low sensitivity

ST T changes The ST T changes utilized as criteria of LVH are generally thought to be secondary to heart disease rather than primary indicators of increased muscle mass. [1 71 72] This is borne out by the longitudinal study of LVH[7] and by the study of athletes [73] It is also indicated by the occurrence of similar changes in the absence of hypertrophy the so-called strain pattern [72 7] although this term is sometimes used to imply LVH [71 63 71 73] Probably many of the observed changes are ischemic in origin [17 72 71] In any case it is generally agreed that ST T changes are rather non-specific.[7 1 3 69]

QRS voltage criteria It seems intuitively obvious that a bigger heart would generate a stronger electric field but attempts to explain this relationship in more sophisticated terms have not contributed particularly to our understanding of it. Carter and Estes found that a positive correlation existed between heart weight and increased voltage only when heart weight exceeded Zeek's[9] definition of normal and concluded that the relationship was not a direct one and that some other factor associated with heart disease may be more important. However this does not seem a necessary conclu

sion because other random effects were presumably operative for example a large subject could have a correspondingly large heart but be similarly proportioned to a small subject with a small heart so that the potentials at the body surface could be approximately the same Carter and Estes do not seem to have *allowed for body size* in this part of their comparison That a disease process is not required to give large voltages has been demonstrated in athletes presumably due to physiologic hypertrophy [72,81-83]

The usefulness of the voltage criteria in the diagnosis of LVH is, therefore not unexpected but the correlation between increased voltage and increased heart weight at autopsy has been disappointingly low Why is this? It will be suggested in this communication that (1) misleadingly low correlations between the ECG and PM diagnoses of LVH may derive from technical difficulties in the taking of an ECG and (2) these correlations were made worse by the utilization of an autopsy criterion of normality which may falsely exclude heart weights that are actually normal.

Technical difficulties relating to the ECG

Various voltage criteria proposed for the diagnosis of LVH are presented in Table I These all require the careful measurement of the amplitudes of QRS deflections, *generally to the nearest millimeter* although measurements have been made to the nearest 0.5 mm [17] Many studies have employed conventional direct writing electrocardiographs, but with these instruments, errors in QRS voltage readings can exceed 11 per cent in 50 per cent of the cases and errors over 50 per cent may be encountered even though the instruments may appear to be operating normally [78,84] Unless a check on the response of an electrocardiograph to rapid signals is made QRS voltage readings cannot be trusted Therefore it may be assumed that determinations of normal limit based on direct writer studies are liable to be seriously disturbed by random instrument variation. An expected result of this would be a lowering of the observed correlation between QRS voltage measurements and heart weight. A positive correlation would still be observed but this would tend to apply to rather gross changes. It is difficult to say how important a role instrument error has played because most reports do not indicate the types of instrument employed A spike response tester (available commercially) *has been described which makes it possible* to check the high frequency response of an electrocardiograph easily and quickly [87] The above criticism applies to direct writing electrocardiographs, but other types of instrument may show inadequate high frequency responses, e.g string galvanometers used with inadequate skin preparation. Einthoven's suggested deflection time of 10 msec.[39] gives an upper cut-off frequency of approximately 30 Hz, which is certainly inadequate [78,84] Even instruments with an intrinsically good response may have this intentionally spoiled by the manufacturer in order to reduce line frequency interference a filter is installed to be switched in or out by the operator This makes it easier to obtain 60-cycle free records and so is apt to be left in for all cases.

Voltage determinations in unipolar leads are subject to a further distortion unbalancing of the central terminal resistors due to unequal skin-electrode resistances.[43,44] This effect is likely to be particularly troublesome in leads aV aV L and aV and with electrocardiographs with central terminal resistors of only 5 000 ohms. Ac*tually even 100 000 ohms is too low and* buffer amplifiers should be used ahead of the resistors.

The removal of all the technical problems—which would not be difficult—would not necessarily result in an immediate improvement in the diagnosis of LVH because of doubts concerning the performance of the instruments employed by those workers whose criteria we now use. Nevertheless, the employment of superior instruments is an essential first step

Postmortem criteria of LVH

The various *autopsy criteria for LVH* may be classified as depending on measurements of ventricular wall thickness, [4, 11, 23] on weights of the ventricles, [14, 17, 23, 26, 32] or on total heart weight. [6-10, 22, 26, 27, 34] Measurements of the ventricular

Table 1 Part 1 QRS voltage and autopsy criteria used in various ECG-PM correlation studies of left ventricular hypertrophy

Author(s)	QRS voltage criteria code numbers	PM criteria	Type of ECG recorder
Carter and Estes	42	Heart weight > Zeek upper limit of normal	Not stated
Chou and associates	3 4 6 16 26 33	Heart weight > Zeek upper limit of normal and LV wall thickness ≥ 13 mm	Not stated
Griep	2 6, 26 33–36	Heart weight/body weight > 0.5 per cent and heart weight > Zeek upper limit of normal	Not stated
Rosenfeld and associates	2 6 or 18, 26 33	Heart weight > Zeek upper limit of normal and LV wall thickness > 14 mm and RV wall thickness < 4 mm	Not stated
Scott and associates[14]	3–5 7 9 13 14 16 17 19 24 26 31 33 35 36	Heart weight > Zeek upper limit of normal, and LV wall thickness ≥ 13 mm and RV wall thickness ≤ 4 mm	Not stated
Selzer and associates[80]	2 4 5 7 10, 15 18, 24 6 31 33 35 37	Heart weight > Zeek upper limit of normal plus 25 Gm	String galvanometer
Wolff and associates[34]	41	) Corrected heart weight > Zeek upper limit of normal (= mean + 1 S.D) and LV wall thickness ≥ 18 mm. b) Corrected heart weight > Zeek mean + 2 S.D and LV wall thickness ≥ 16 mm. and RV wall thickness ≤ 4 mm or) Corrected heart weight > Zeek mean + 3 S.D	Direct writer
Allenstein and Mori[7]	1 3 4 8 9 13 15 16 19 24 26 31 33 36	LV wall thickness ≥ 13 mm and RV wall thickness ≤ 3 mm.	Direct writer
Berthaux and associates	5 20 22 25 30	a) Weight of LV/body weight ≥ 0.30 per cent or b) Weight of LV > 150 Gm	Photographic device in great majority of cases
Kalliomaki and associates[11]	2 26 33 36	LV wall thickness > 15 mm	Not stated
Kommans and associates[14]	2 26, 30 37 39	Weight of LV > some value between 126 Gm and 138 Gm	Not stated

Table I Part I—Cont'd

Author(s)	QRS voltage criteria code numbers*	PM criteria	Type of ECG recorder
Mazzoleni and associates[34]	40	Men Weight of L.V. + weight of interventricular septum > 203 Gm. and $\frac{\text{Weight of L.V. + weight of I.V.S.}}{\text{Weight of R.V.}} > 3.8$ Women Weight of L.V. + weight of interventricular septum > 141 Gm. and $\frac{\text{Weight of L.V. + weight of I.V.S.}}{\text{Weight of R.V.}} > 4.0$	Direct writing and photographic instruments
McPhie[13]	2, 12, 26, 33 36–39	Total ventricular weight > 250 Gm.	Direct writer
Selzer and associates[30]	Same as Selzer and associates[30]	Heart weight > 400 Gm. with L.V. wall thickness ≥ 15 mm., and L.V. wall thickness/R.V. wall thickness > 3.1	String galvanometer then later a direct writer
Selzer and associates	26	Heart weight ≥ 500 Gm.	String galvanometer
Vlaoli and associates[34]	43	Weight of L.V./weight of R.V. > 1.66 ± 0.32	Not stated
Zapf and associates[33]	2 21 23 26–29 33	a) Heart weight > 500 Gm. with $\frac{\text{Weight of R.V.}}{\text{Weight of L.V.}} < 0.4$ or b) Heart weight/body weight > 0.65 per cent with weight of R.V./weight of L.V. < 0.4	Not stated

Table 1 Part 2 QRS voltage and autopsy criteria used in various ECG-PM correlation studies of left ventricular hypertrophy

Limb leads		Precordial (chest) leads	
Code No	*Criteria*	*Code No.*	*Criteria*
1	$R_I + S_{III} \geq 2\ 5$ mv	20	Lewis index > 1 6 m
2	$R + S_{III} > 2\ 5$ mv	21	Lewis index > 1 7 mv
3	$R + S_{III} > 2\ 5$ m with associated LAD	22	$S_{V1} > 2\ 5$ mv
4	Q or $S_{aVR} > 1\ 4$ m	23	S_V or $V > 2\ 6$ mv
5	$R_{VL} > 1\ 1$ mv	24	$R \leq 0\ 1$ m $+ S_V \geq 2\ 4$ mv
6	$R_{VL} > 1\ 1$ mv in horizontal heart	25	$S_V + R > 3\ 5$ mv
7	$R_{aVL} > 1\ 2$ mv	26	$S_{V1} + R$ or $> 3\ 5$ m
8	$R_{aVL} > 1\ 2$ mv in horizontal heart	27	S_{V1} or $+ R$ or $> 3\ 5$ mv
9	$R_L \geq 1\ 3$ mv in horizontal heart	28	S_V or $+ R$ or $> 3\ 5$ m if or $\leq 0\ 2$ m
10	$R_{aVL} > 1\ 3$ mv	29	S_V or $+ R$ or $> 4\ 5$ mv
11	$R_L > 1\ 0$ mv T/R < 10 per cent	30	$R > 2\ 5$ mv
12	$R_{aL} > 1\ 1$ mv or $R_a > 1\ 0$ mv T/R < 10 per cent with horizontal or semihorizontal heart	31	$R_{V5} \geq 3\ 3$ mv
13	$R_a > 1\ 1$ mv T/R < 10 per cent or T/R > 10 per cent or $R_{VL} > 1\ 0$ to $1\ 1$ mv T/R < 10 per cent (with a horizontal or semihorizontal heart)	32	$R \geq 2\ 6$ mv
14	$R_{aVF} > 1\ 9$ mv	33	R or $V > 2\ 6$ m
15	$R_{aVF} > 1\ 9$ mv in vertical heart	34	$R_V > R$
16	$R_{aVF} \geq 2\ 0$ mv in vertical heart	35	$R/T \geq 10$ in V5 or V6
17	$R_{aVF} > 2\ 0$ mv	36	$\frac{R/S \text{ in } V5}{R/S \text{ in } V1} > 100$
18	$R_a > 2\ 0$ mv in a vertical heart	37	(Greatest R + greatest S) in V leads > 4 5 mv
19	Neg VR + pos. VL(F) > maximum normal limit depending on respective "electrical" position[11]	38	(Greatest R + greatest S) in V leads > 4 0 mv
		39	(Greatest R + greatest S) in V leads > 3 5 mv

*Code numbers for QRS voltage criteria of left ventricular hypertrophy

Table 1 Part 2—Cont'd

Limb leads		Precordial (chest) leads	
Code No.*	Criteria	Code No.	Criteria
40	For the following, arious upper limits were tested in the ranges given Lewis index < −1 4 to > +1 7 mv R > 0 75 t > 1 5 mv S_{III} > 1 0 to > 2 5 mv S_1 > 1 5 to > 3 0 mv R > 1 0 to > 2 5 mv R > 1 0 t > 2 5 mv S_1 + R > 2 55 t > 3 5 mv Largest (R + S) in y one hest lead ≥ 2 01 t ≥ 4 01 mv	42	For the following no limits were necessary for the correlation study R R_{II} or R S amplit de in right precordial leads R mplitude in left precordial leads
41	I or the following arious age-dependent pper limits were tested I the ranges given Lewis index > 1 7 m R > 0 58 t > 1 01 mv S_V > 2 00 to > 2 51 m S_{V1} > 2 54 to > 4 55 mv R > 2 07 to > 2 60 m R > 1 90 t > 2 44 m S_1 + R > 3 5 t > 4 0 mv	43	For the following no limits were given Sokolow index (S_{V1} + R v) Blondeau index (given as S_{V1} + R_{V1}) Lewis (White and Bock) index (R_I + S_I) − (R_{III} + S_I) Jinich index (VL + VF⁻) − (VI + VL⁻) (R v + S_{V1}) − (R + S_{V1})

*Code numbers for QRS oltage riteria of lef ventricular hypertroph

wall thickness vary according to where they are made, e.g., the relatively thin wall at the apex of the left ventricle, the obliquity of the cut, the inclusion of trabeculae or papillary muscles, and the presence or absence of dilatation. Although commonly used, some authors consider measurements of wall thickness quite useless.[illegible] Weighing the left ventricle alone requires separation of the septum into right and left portions,[illegible] which can be difficult,[illegible] or a decision to include the whole septal mass[illegible] or to treat it separately.[illegible] Unfortunately, the procedure is not standardized and most ECG-PM correlation studies must be based on whatever examination of the heart happens to be routine at the institution concerned. However, whatever else is done, the heart is generally weighed whole since this can be done easily and accurately, although even here contributions from epicardial fat and attached vessels are variables which are handled differently in various studies.[illegible] The problem is not merely one of deciding on the best measurements to adopt; ranges of normal values must be established.

The establishment of normal values from autopsy material requires a long period of time and a great deal of work, which is rendered more difficult since the introduction of chemotherapeutic and antibiotic agents and the resulting decline in number of deaths from acute infections. The largest series was reported by Zeek,[illegible] who selected normals from nearly 10,000 autopsies carried out between 1924 and 1940. Zeek decided to correlate total heart weight (HW) with body length (BL) rather than body weight (BW) because of the variability of the latter in many antemortem conditions and because it is easier to measure the length of a cadaver than to weigh it. From her linear regression analysis of HW on BL in normally nourished adults—357 males and 224 females—she derived a table of normal values which has been widely used in ECG-PM correlation studies (Table I). The coefficients of correlation were rather low, r = 0.33 for males and 0.29 for females. This indicates that BL [illegible] ndication [illegible] ut it is [illegible] better taking BL into consideration could affect the diagnosis of marginal hypertrophy in short or medium length cadavers.

Rosahn[illegible] studied 187 men who had died from trauma, acute infections, etc., with presumably normal hearts and terminal body weights and tested the linear regressions between HW and BW, age, body length, surface area derived from BW and BL, and BW/BL. He failed to find a significant correlation between HW and BL; the coefficient of correlation, r, was 0.12. This is in contradiction to findings of Zeek, to our analysis of Zeek's data (see Appendix I) and to the findings of Tardini and associates,[illegible] whose analyses of 200 normals yield r = 0.53 for men and r = 0.44 for women for the linear regression of HW on BL. Rosahn found a low positive correlation between HW and age (r = 0.27), but admits this could have been due to unintentional inclusion of hypertensives in the group of older subjects—Smith[illegible] reported that HW did not increase with age. There would seem to be no physiological reason why the heart of a healthy man would increase with age; on the contrary, as activity became less, a slight decrease might be expected.[illegible] It is of interest to note that the mean HW in Rosahn's series was somewhat higher than in other comparable series, viz., 356 vs 319 grams for Zeek's males, a similar figure indicated by Tardini and associates[illegible] in their graph, 321 grams found by Aschoff[illegible] in 685 soldiers, and 335 grams found by Greenwood and Brown[illegible] in 78 rigorously selected individuals in about the same average age group as Rosahn's group. Actually, Rosahn quotes the average HW found by the latter authors as 371 rather than 335 grams, on the assumption that the authors used apothecaries' ounces (1 oz. = 31 Gm.) whereas it is much more likely that avoirdupois ounces were used (1 oz. = 28 Gm.).

Gray and Mahan[illegible] considered that an analysis based on the linear regression of log HW on log BW might be helpful. They tested the following four equations: (1) the equation derived from the linear regression of log HW on log BW for 1,056 male cases culled from the literature; (2) the equation derived from the same analysis of Rosahn's 174 males—they were given his raw data; (3) Rosahn's linear regression equation of HW on BW for his 174 males; (4) Zeek's

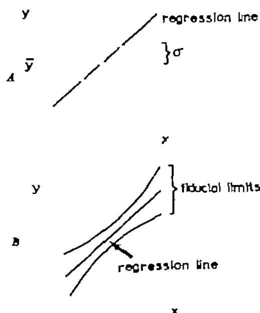


Fig. 1. A, See text. B, See text.

linear regression equation of HW on BL for her 357 normally nourished males. The four equations were used to predict the heart weights of 40 of the cases in Rosahn's series. They concluded that Zeek's formula for predicting heart weights in males was the best. This endorsement, following as it did soon after Zeek's paper and not long after the paper by Rosahn, probably did much to promote the wide acceptance of Zeek's table of normal values. Unfortunately, Zeek's formula for females was not tested and neither was her table of normal values for males and females. Our analysis of Zeek's raw data (see Appendix I) agrees reasonably well with her formula for males but not with that for females. A curious point, not explained by Gray and Mahan, is the discrepancy between Rosahn's finding that a significant correlation between HW and BL did not exist and their finding that Zeek's formula for males, which was of course based on such a correlation, performed better than their log-log formula which in turn performed better than Rosahn's formula relating HW to BW, even though a subgroup of Rosahn's own cases was used for the comparison. Unhappily, Dr. Rosahn's raw data have been lost, so this discrepancy must remain unexplained.

Dr. Zeek Minning has graciously supplied us with her raw data to run a computer analysis to seek improvement in the definition of normal HW required for setting up polarcardiographic criteria for LVH.[41] Our analysis, based on ungrouped data, confirms Zeek's finding of a significant correlation between HW and BL. However, although we obtain an essentially similar linear regression of HW on BL for males, with $\sigma = 38.0$ Gm. about the line and $r = 0.38$, we do not confirm her analysis for females (see Appendix I). Whereas she obtained values of $\sigma = 30$ Gm. and $r = 0.29$, we obtain $\sigma = 39.6$ Gm. about the line and $r = 0.31$, i.e., values closer to those found for the males. The correlation between HW and BW could not be tested because BW's were not available.

The raw data were also used to test Zeek's table of normal heart weights (see Appendix I). It was found that 98 of the 357 normally nourished males, or 27 per cent, and 106 of the 224 normally nourished females, or 47 per cent, actually fell outside the bounds for HW indicated by the table derived from these very cases. This paradox resulted from Zeek's use of one standard deviation for setting the limits in the table rather than two, and from her low value of σ for the females.

For the diagnosis of hypertrophy one is concerned only with the upper bound of normality. The upper bounds of normal heart weights indicated in Zeek's table were exceeded by 44, or 12 per cent of the males, and by 54, or 24 per cent of the females in the series of normals on which the table was based. It follows that a definition of hypertrophy based on Zeek's table will include a considerable proportion of cases with non-hypertrophied hearts. If the ECG criteria for hypertrophy are not present in these cases—as well they might not be—the cases would appear as ECG false negatives. Therefore, attempts to test ECG criteria against such a definition of normal are apt to indicate rather low sensitivity—or, if the sensitivity is raised to include these cases, other normal cases not diagnosed as hypertrophy from the table will probably be included, which will give a rather low specificity.

The role of Zeek's table on the ECG diagnosis of LVH may be judged from Table I

which lists the authors who have used it. A notable exception is the work of Marzolini and associates who employ their own criteria. However these appear to be based on a normal series of only 26 males and 19 females.[1b]

A simple PM index of hypertrophy. A satisfactory definition of normal HW is clearly needed. Obviously some correlation must exist between body size and HW. The question is: What correlate of body size should be used: BL, BW, or surface area? Zeek's point that BL is less affected than BW by terminal conditions appears valid and in any case cadavers are not usually weighed. Rosahn suggested the use of the subject's normal BW but this, of course, poses difficulties too. What is the "normal" weight of a patient who is normally obese? Surface area, since it is derived from tables based on BW and BL, does not avoid these difficulties with respect to BW. Therefore it appears to us that perhaps BL is the most practical choice of a correlate.

As indicated in Appendix II the regression lines of HW on BL for Zeek's men and women may be assumed to pass through the origin. This makes it permissible to express the relationship between HW and BL simply by their ratio. The HW/BL ratios were calculated for each case and upper bounds were obtained for the two sexes by determining the upper 5-percentile points, according to the method of Simonson.[99] We have employed the upper 5-percentile point rather than the lower and upper 2½-percentile points because we are only interested in an upper bound for normal heart weight. Unlike methods depending on a regression analysis, the determination of upper bounds by this method does not assume a gaussian distribution. On the other hand, since it does not give σ, it does not provide an indication of the degree of scatter of the data. For our purpose this is unimportant.

For Zeek's 357 males and 224 females, which represent normally nourished subgroups of her totals of 523 males and 403 females, the upper 5-percentiles of the HW/BL ratios are 2.20 Gm. per centimeter and 2.06 Gm. per centimeter, respectively. It is of interest that even if the restriction of normal nourishment is not applied, and 5-percentiles are obtained for the sets of 523 males and 403 females, almost identical ratios are obtained.

The lower bounds for Zeek's normally nourished cases turn out to be 1.47 Gm. per centimeter for males and 1.24 Gm. per centimeter for females for the 5-percentile points. Published data by Hellerstein and Santiago-Stevenson[100] of the HW, BW, and BL in 85 cases diagnosed as cardiac atrophy show HW/BL ratios with an upper 5-percentile of 1.64 Gm. per centimeter.

Having a simple upper bound for HW/BL facilitates the correlation of other factors not dependent on body size with hypertrophy. As an example, suppose hypertrophy is being correlated with blood pressure. If blood pressure is plotted against HW/BL rather than HW, we have in effect normalized the body size parameter of the group. In addition to body size a factor relating to body build, e.g., ponderal index, may be introduced.

The ponderal index, defined as

$$PI = BL/\sqrt[3]{BW}$$

is a useful index of body build because it is independent of body size. It is much more meaningful than tall, medium, thickset, etc. Although it has been employed in anthropomorphic studies for many years,[101-110] its appearance in medical literature has been relatively recent.[111]

If it is true that in a healthy individual HW does not increase after say 25 years of age,[31] PI at this age could be used to obtain an upper bound for normal HW without the complications of morbid conditions affecting BW. The formula would be

$$HW = k \times PI \times BW$$

$$= k \times BL \times BW^{2/3}$$

Since BW is not available in Zeek's data we cannot provide a figure for k. In a university population employed in a previous study,[112] the upper and lower 2½-percentiles of PI for 119 males were 14.00 and 12.28, and for 74 females, 13.64 and 11.54.

Summary

Review of the literature has brought out the following: (1) ECG criteria for LVH commonly give false positives and false negatives. (2) Although LAD, prolonged VAT, and ST-T changes may be of value

the most useful are the voltage criteria of which there are many (3) Low correlation between increased voltage and increased heart weight at autopsy may derive from technical errors in ECG recording that arise from the equipment used and the use of criteria of normality which may exclude heart weights which are actually normal. (4) Examination of postmortem criteria of normality reveals that a satisfactory definition of LVH does not exist.

A simple index of hypertrophy based on a reanalysis of data on 926 normal cases is proposed HW/BL > 2.20 Gm. per centimeter for men and >2 06 Gm. per centimeter for women.

Appendix I

1 From 9 676 autopsies, Zeek selected 926 adult cases in which the hearts were considered clinically and pathologically normal. Of the 523 males and 403 females there were 357 males and 224 females who were normally nourished The HWs and BLs of each of the 926 cases were very kindly supplied to us by Dr Zeek (now Dr Zeek Minning) Statistical analysis was carried out at the Computing Center of the University of British Columbia.

For the 357 normally nourished males, the ungrouped data yielded the following linear regression of HW on BL

$$HW = 2.0085\, BL - 23.8319 \quad \sigma = 38.012$$

The arithmetic mean heart weight was 319.2377 Gm with a standard deviation about the mean of 40 9352

For the same regression Zeek grouped the data—manual computations from ungrouped data would have been excessively tedious—and obtained

$$HW = 1.9\, BL - 2.1 \pm 40$$

Actually this agrees quite well with the computer result, when the distance of the plots from the origin is taken into account—minima for HW and BL were 200 Gm and 142 cm Th differences between the equations were due to grouping the data and rounding off during computation.

For the 224 normally nourished females the corresponding regressions were

$$HW = 1.7300\, BL - 13.8486 \quad \sigma = 39.573$$

In association with J. R. H. Dempster Ph.D.

with an arithmetic mean heart weight of 262.0987 Gm. and a standard deviation about the mean of 41 4271 obtained from the computer analysis of ungrouped data compared with

$$HW = 1.78\, BL - 21.58 \pm 30$$

reported by Zeek. Here the discrepancies could not be accounted for by the grouping of the data or rounding off

2 In the table of normal heart weights published by Zeek [11] the indicated allowable spread excludes 98 of the normal males (27 45 per cent) and 106 of the normal females (47.32 per cent) on which the table was based. The larger percentage of females excluded derives from the lower value of σ that was used It is common practice to set range limits to embrace 95 per cent of the normal population. [36] To achieve this the allowable spread would be $\pm$ 1 97 σ rather than $\pm\ \sigma$ For justification for the use of σ to give tolerance limits, see Appendix II (*1*)

3 Intuitively one might expect that the heart weight would vary as the cube of body length The possibility that the regressions of Y i.e. HW on X i.e. BL, raised to some power might reduce the limits of normal was therefore entertained. However the computer yielded *almost* identical correlation coefficients between Y and X X^2 and X which indicates that regression of Y on X^2 and X will be essentially *similar to that on* X. The correlation coefficients obtained from the analyses in §*1* above were $r = 0.3754$ for the males and $= 0.3079$ for the females. Corresponding figures reported by Zeek were $= 0.33$ and $= 0.29$

4 If the regression line for Y and X can be assumed to pass through the origin the data may be handled in a simpler manner which has certain advantages.

For justification of this assumption see Appendix *II (2)*

A simple definition of hypertrophy Using

$$\frac{HW}{BL} = k$$

we can seek the limits of k to include 95 per cent of the population. The ratio k, was determined for each of Zeek s cases and the results were printed out in order of increasing magnitude. Normal limits were d

termined from the percentile distribution according to the method of Simonson.[18]

Since our interest is in the definition of hypertrophy based on heart weight we require an upper bound for normal such that 95 per cent of cases will fall below it. This is the upper 5-percentile.

For the 357 normally nourished males the upper 5-percentile is 2.1965 Gm. per centimeter. If this is rounded off, we have

$$\frac{HW\ (Gm.)}{BL\ (cm.)} > 2.20 \text{ Gm. per centimeter for men}$$

as a definition of hypertrophy in normally nourished males. This definition does not assume a gaussian distribution. Furthermore it avoids the unsatisfactory condition in which heart weights for different body lengths have equal limits, as was the case with Zeek's table. However, it might be considered unsatisfactory to apply to individuals who were at either extreme of BL if it turned out that the normal cases excluded by it were either mostly short or mostly tall. The 18 cases excluded from the 357 males had the following BLs arranged in order of decreasing values of k: 161, 162, 164, 154, 185, 170, 168, 170, 179, 179, 173, 180, 185, 163, 170, 161, 161, and 175. The range for the 357 cases is 142-204 with an arithmetic mean of 170.8. The arithmetic mean for the above 18 cases is 169.9. This is satisfactory.

For interest, the corresponding upper and lower 2½-percentile points were determined and these are 2.235 grams per centimeter and 1.415 grams per centimeter.

For the 224 normally nourished females the upper 5-percentile is 2.058 grams per centimeter, giving the following definition of hypertrophy:

$$\frac{HW\ (Gm.)}{BL\ (cm.)} > 2.06 \text{ Gm. per centimeter for women}$$

The 11 cases excluded by this definition had the following BLs arranged in order of decreasing values of k: 152, 146, 158, 161, 152, 164, 165, 160, 161, 153, and 170. The range for the 224 cases is 135-178, with an arithmetic mean of 159.5. The arithmetic mean for the above 11 cases is 158.4. This is satisfactory since it indicates that cases are not penalized for tallness or shortness.

The upper and lower 2½-percentile points for the females are 2.133 grams per centimeter and 1.209 grams per centimeter.

Although Zeek's definition of normal and the above percentile analysis were restricted to cases being normally nourished, it is of interest to see what happens if the definitions are obtained from all Zeek's normals, i.e., 523 men and 403 women. For the 523 men the upper 5-percentile of HW/BL is 2.194 grams per centimeter, which excludes 26 cases as shown in Table II. The rareness of "hypertrophy" in the emaciated group is striking. That this is due to absence of epicardial fat in this group immediately comes to mind; however, Dr. Zeek Minning does not believe this is the correct explanation.[19] Perhaps the relationship between cardiac atrophy and wasting diseases provides a clue.[20,21] It is of interest that Amad and associates[22] found that the heart weights of 12 subjects with marked chronic obesity exceeded expected values and that epicardial fat represented no significant contribution in most instances; fatty infiltration was seen in only one case.

The usefulness of the definition of hypertrophy given above, viz.,

$$\frac{HW}{BL} > 2.20 \text{ Gm. per centimeter}$$

is, fortunately, not restricted to the normally nourished because if it is applied to the 523 cases, the same 26 cases as appear in Table II are excluded. However, Table II indicates that muscular or obese men tend to have bigger hearts than emaciated men.

Table II. Cases exceeding the upper 5 per centile for the ratio HW/BL in 523 cases of Zeek's normal males

Group	No. of cases in group	No. of cases excluded by HW/BL < 2.194 Gm./cm.
Normal	357	18
Emaciated	136	1
Muscular	12	3
Obese	18	4
	523	26

Appendix II

1 *Justification for use of σ to give tolerance limits* We require not fiducial limits which indicate the bounds between which the true regression line lies but tolerance limits, which indicate the bounds between which a new individual value of y lies.[11a]

Tolerance limits of HW for a given x or BL are

$$y_L = Y \pm t\sigma \sqrt{1 + \frac{1}{n} + \frac{(x - \bar{x})}{\sum (x - \bar{x})}}$$

where y_L is the range of HW Y is the HW on the regression line, t is Student's t with n-2 degrees of freedom σ is the sample standard deviation from regression n is the sample size and x is the arithmetic mean of the sample BLs.[11] In this equation the second and third terms within the square root become negligible using our data because n is large and

$$\sum (x - \bar{x}) >> (x - \bar{x})$$

At the 5 per cent confidence level (two-tailed) t = 1 97 so

$$y_L = Y \pm 1\ 97\ \sigma$$

2. *Test of the hypothesis that the intercept of the regression line is zero*[11a,11] If the equation of the regression line is given by

$$y = a + b\ (x - \bar{x})$$

corresponding with

$$\eta = \alpha + \beta\ (x - \bar{x})$$

assumed for the parent population then η is the expected value of y

For one particular x_o

$$\sigma_{yo} = \sigma + (x - \bar{x})\ \sigma_b \qquad (1)$$

The values of and σ are defined by

$$\sigma = \frac{\sigma}{n}$$

and

$$= \frac{\sigma}{\sum (x - \bar{x})}$$

*In association with J R. H. Dempster Ph D

where σ^2 is the variance of the parent population on the regression line.

$$\sigma_{yo} = \sigma \left[\frac{1}{n} + \frac{(x - \bar{x})}{\sum (x - \bar{x})}\right] \qquad (2)$$

The variate y is a linear function of a and b themselves linear functions of the y_i the observed values in the sample. The y_i are assumed to be normally distributed Therefore, y is normally distributed These conditions allow a t test with n 2 degrees of freedom to be set up

Inserting s for σ and s_{yo} for σ_{yo}, where s_{yo} is the estimated variance of y from the sample we get

$$\frac{y - \eta}{s_{yo}} \sim t \qquad (3)$$

To test the intercept, we have

$$\frac{y_{x=0} - \eta_{x=0}}{[s_{yo}]_{x=0}} \sim t \qquad (4)$$

The computer calculated from Zeek's raw data for the 357 males

$$y_{x=0} = -23.8319$$

$$s = \sqrt{1445}$$

$$\bar{x} = 170\ 8151$$

and

$$\sum (x - \bar{x}) = 20{,}863\ 9782$$

Continuing as in the example given by Brownlee [9] it follows that for $x_o = 0$

$$\left[s_{yo}\right]_{x=0} = s\left[\frac{1}{n} + \frac{\bar{x}^2}{\sum_1 (x - \bar{x})}\right]^{\frac{1}{2}} \quad (r.s\ )$$

$$= \left[(1445)\left(\frac{1}{357} + \frac{(170\ 8151)}{20{,}863\ 9782}\right)\right]^{\frac{1}{2}}$$

$$\simeq 45\ 0$$

Under the hypothesis that $(\eta)_{x=0} = 0$ we get using (4) $t_{35} = \frac{-23.8319}{45} = -0\ 5296.$

Since the 5 per cent confidence level for this t is 1 97 and since 1 97 > −0.5296 the hypothesis is acceptable for a zero intercept.

For confidence limits of zero intercept

$$\eta = \gamma \pm \sigma_{\gamma} t$$
$$= -23.8319 \pm 1.97 \ (45)$$
$$= -112.48 \text{ or } 64.82$$

It is, therefore permissible to use the equation

$$\frac{HW}{BI} = k$$

A similar conclusion would apply to the females.

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The Polarcardiograph Diagnosis of left ventricular hypertrophy

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The Polarcardiograph gives the direction and magnitude of the heart vector as continuous tracings known as polarcardiograms (PCGs).[1] In the diagnosis of infarction the superiority of the PCG over the single electrocardiogram (ECG) recorded at the same time has been demonstrated;[2] in a group of autopsied cases the PCG was found to be almost twice as sensitive an indicator of infarction.

In the ECG the large QRS amplitudes associated with left ventricular hypertrophy (LVH) are manifestations of an increase in the spatial magnitude of the heart vector. Gamboa and associates[3] have shown that the magnitude of the maximum heart vector correlates strongly with maximum systolic pressure in the left ventricle and hence with various forms of pressure overload. Since the PCG displays the magnitude of the heart vector as a time graph, it should provide a simple indication of LVH.

What is LVH? It seems almost axiomatic that the most rigorous definition of LVH would be made on anatomic grounds. Perhaps the most widely used postmortem (PM) criteria of LVH are those based on upper bounds for heart weight for various body lengths reported by Zeek[4] for a large series of normal men and women. Reexamination of Zeek's raw data by Dower and associates,[5] while it confirmed her finding of a significant correlation between heart weight and body length, disclosed that her table excluded 27 per cent of her normal men and 47 per cent of her normal women. Use of these criteria would therefore give rise to a high incidence of false positives in the PM diagnosis of LVH. Reanalysis of Zeek's data yielded a simple index of hypertrophy, the heart weight/body length ratio (HW/BL). The upper 5-percentile points were 2.20 Gm. per centimeter for men and 2.06 Gm. per centimeter for women (Table I). These figures will be used as an anatomic definition of LVH in this paper.

The diagnosis of LVH from the ECG hinges largely upon the so-called voltage criteria.[6] However, the popular choice of ECG criteria for LVH seems to pose somewhat of a problem. Dower and associates reviewed 17 studies of the correlation between the diagnosis of LVH on ECG and PM grounds which disclosed that 43 different voltage criteria were used, although the differences between some of these were

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small. The ECG voltage criteria employed in the present paper appear to be fairly representative.

In this communication PCG criteria for the diagnosis of LVH will be proposed on the basis of a study of normal cases. The PCG, ECG, and LM diagnoses of LVH will then be compared. A sample of cases meeting the PCG criteria for LVH with clinical evidence of pressure overload will then be used to illustrate typical features of LVH in the PCG.

Method

Technique. The technique of recording PCGs, using the Frank lead system, has been previously described. The tube model of the polarcardiograph was used for the veterans and the transistorized model was used for the university volunteers (UBC). ECGs were obtained with direct writing electrocardiographs of the hot stylus type. Because of the tendency of many direct writers to yield misleadingly low QRS responses, especially when their upper cut-off frequency falls below 50 Hz, the instruments were checked from time to time with a spike response test.[14]

Autopsies were in general witnessed by at least one of the authors. Although measurements of ventricular wall thickness and of the weights of the left and right ventricles and the interventricular septum were recorded, it was decided, for reasons given elsewhere, to use simply the total heart weight (HW) divided by the body length (BL) to indicate LVH, no distinction being made between LVH and combined hypertrophy.

Selection of cases. Samples were taken from two different populations: male and female volunteers on a university campus (UBC) and males in a veterans hospital. The UBC population gave two samples, 121 men and 74 women whose mean ages were 25.3 years and 23.9 years, respectively. The age distributions of these samples have been given in a previous report. For the statistical reasons given in that report, medical factors were not considered in the selection of cases in these two samples. The veterans hospital population gave a sample of 192 men whose mean age was 58.6 years. The age distribution of this sample has also been given in a previous report. The cases in this sample were selected on the basis of normality of their electrocardiograms. To the extent that the ECG definition of normality imposes a limit on peak QRS voltages, PCG criteria of LVH based on this sample are subject to the errors pertaining to the ECG diagnosis of this

Table 1. Diagnosis of ventricular hypertrophy. Percentiles in samples from various normal populations

Index of hypertrophy	No. of cases	Sex	Source	Percentiles: Lower 2½	Percentiles: Upper 2½	Percentiles: Upper 5
HW/BL (Gm./cm.)	357	M	Zeek*	1.42	2.24	2.20
HW/BL (Gm./cm.)	224	F	Zeek*	1.21	2.13	2.06
MR (mv.)	121	M	UBC†	0.95	[illegible]	1.90
MR (mv.)	74	F	UBC†	0.75	2.17	1.82
MR (mv.)	192	M	Veterans‡	0.69	2.03	1.92
tmR (mv.)	[illegible]	M	UBC	0.77	1.68	1.59
tmR (mv.)	74	F	UBC	0.56	1.40	1.28
tmR (mv.)	184§	M	Veterans	0.57	1.87	1.78

*Normally nourished autopsied cases with normal hearts (see Reference No. 5).
†Young adult volunteers from UBC campus.
‡Elderly patients with normal ECGs at Shaughnessy Veterans Hospital.
§In 8 cases in the sample of veterans, tmR was not available.

condition. For this reason the findings in this sample will be presented merely for the purposes of comparison.

Results

Upper bound of normal maximum QRS vectors. For the samples studied the maximum spatial QRS vector $\hat{R}$ has a magnitude MR with the frequency distributions shown in Fig. 1. In the UBC sample the distributions for the 121 men and 74 women are very similar but the distribution for the men is about 0.1 mv. to the right of that for the women. The distribution for the 192 veterans agrees well with those seen for the UBC men and women, especially the latter, but is a little more spread out.

The magnitude of $\hat{R}$ in the transverse plane, tmR, for the above samples has the frequency distributions shown in Fig. 2. The distributions for the UBC men and the veterans are similarly centered but the distribution for the latter is more wide spread. The distribution for the UBC men appears to be about 0.2 mv. to the right of that for the UBC women.

The upper 2½- and 5 percentile points for MR and tmR for the distributions shown in Figs. 1 and 2 are given in Table I. Either percentile point can be used for deriving the PCG criteria for the diagnosis of LVH according to the level of confidence one wishes to accept.[1] We shall employ the 5-percentile points; this means that we anticipate an incidence of false positives of 5 per cent. The upper 5 percentile points for MR for the UBC male, the UBC female, and the veteran samples are 1.90, 1.82, and 1.92 mv., respectively (Table I). The upper 2½-percentile point for the UBC females is 2.17 mv. whereas the corresponding point for the UBC males is 2.11 mv. This is anomalous in view of the general trend for the females to have slightly lower values for MR (Fig. 1). It arises from three cases in the female sample showing relatively large values for MR—exceeding 2.00 mv.—combined with a smaller total number of cases.

The upper 5-percentile points for tmR are 1.59 mv. for the UBC men and 1.28 mv. for the UBC women. This indicates that different criteria in men and women should be used for the diagnosis of LVH based on tmR. It is of interest that the upper 5-percentile for tmR for the veterans, viz. 1.78 mv., considerably exceeds that for the UBC men. However, since the veteran sample could contain cases of LVH which did not show in their ECGs (out of 10

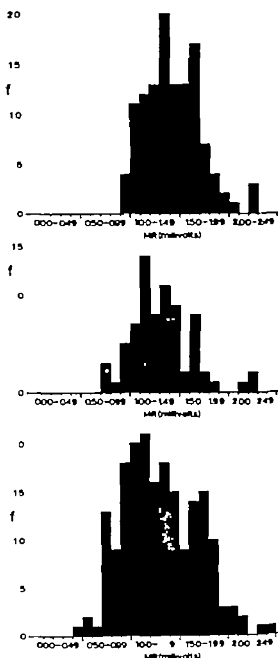


Fig. 1. Maximum spatial QRS vector magnitudes, MR, in 121 young men (A), 74 young women (B), from university campus and 192 elderly men with normal ECGs (C).

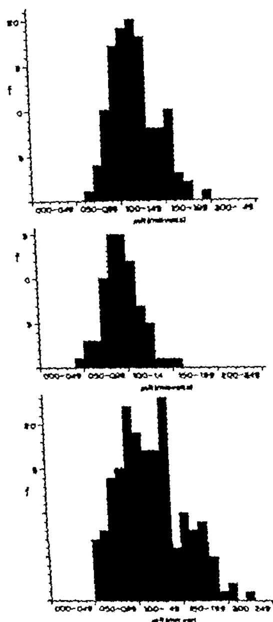


Fig. 2 Maximum transverse-plane QRS vector magnitudes, tmR, in 121 young men (*A*), 74 young women (*B*), from university campus, and 184 elderly men with normal ECGs (*C*).

autopsies in this sample 2 showed LVH) the PCG criteria of LVH should not be based on this higher figure. As already stated the findings in this sample are presented for comparative purposes only

The above results indicate the following criteria for the PCG diagnosis of LVH in men MR > 1.90 mv and/or tmR > 1.59 mv

PCG criteria of LVH applied to 168 autopsies The correlations between MR tmR and HW/BL for 168 autopsies are shown in Figs. 3 and 4 In order to exclude conditions which might yield misleadingly high values for MR and tmR such as left bundle branch block idioventricular rhythms etc. cases were excluded in which the QRS duration exceeded 0.11 second. This measurement was made from the spatial magnitude PCG tracing—the upper 2½-percentile for the QRS duration in normal subjects is 0.108 second In addition the following were eliminated 23 cases for which there existed the possibility that the magnitude outputs had been clipped 1 case in which tumor masses were attached to the heart, and 2 cases in which the subjects were female. Cases diagnosed as LVH on the basis of HW/BL > 2.20 Gm. per centimeter lie above the horizontal dashed line in Figs. 3 and 4. Cases lying to the right of the vertical dashed line in each of the figures exceed the upper 5-percentile points of 1.90 mv and 1.59 mv for MR and tmR, respectively Thus cases in the right upper and left lower quadrants would be correctly diagnosed from the PCG criteria. Those in the left upper and right lower quadrants represent false negatives and false positives respectively To assess the influence of clinical factors graphs were plotted using colors and symbols to indicate the following ponderal index, because of the correlation between electrical axis and build infarctions because infarcted hearts may give lower voltages aortic valve disease and/or hypertension because left ventricular overload should produce hypertrophy and increasing degrees of emphysema, because this might distort the electric field. However these graphs failed to show any significant improvement in the correlations over that shown in Figs 3 and 4.

Figs. 3 and 4 provide a comparison between the PCG and ECG diagnoses of LVH The following ECG diagnostic criteria of LVH were employed $R_{V5} > 26$ mm $S_{V} + R_{V5 \text{ or } V6} > 35$ mm $R_{aVL} >$ 11 mm. $R_{I} + S_{III} > 25$ mm. max. R + max. S(in V_1 to V_6) > 45 mm or $R_{aVF} > 20$ mm. The first five of these were suggested

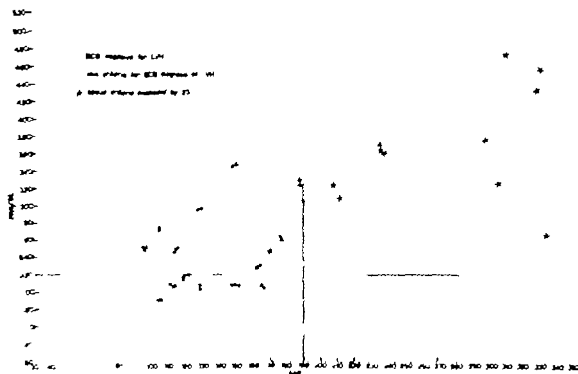


Fig. 3. Relationship between heart weight (Gm.) per body length (cm.), HW/BL, and MR in 168 cases. The dashed lines indicate upper bounds of normal.

Fig. 4. Same as Fig. 3 except that tmR has been substituted for MR.

in a panel discussion[a] and the last was derived from Simonson's[11] book, p. 144. Cases meeting any of these criteria are indicated in Figs. 3 and 4 and those for which any of the criteria were exceeded by more than 25 per cent are further distinguished. In general there is good agreement between the PCG and ECG diagnoses.

Analysis of the correlations between heart weight (HW), HW/BL, MR and tmR was carried out using a standard computer program for linear regression analysis. The results are given in Table II. The strength of correlation is indicated by *r*, the coefficient of correlation. The values of *r* for the four regressions, HW vs. MR, HW vs. tmR, HW/BL vs. MR, and HW/BL vs. tmR, do not differ significantly from 0.5, which is moderate.[a] In a preliminary report on 128 autopsied cases, somewhat higher coefficients of correlation were obtained, viz. 0.54 for HW/BL vs. MR and 0.57 for HW/BL vs. tmR, compared with 0.48 and 0.50, respectively, for the present study (Table II). These discrepancies arise from elimination of 26 cases, for reasons already given, and the addition of 66 new cases.

PCG features of LVH. In order to obtain a comparison of the various quantitative PCG findings seen in LVH with those found in normal cases, a sample was taken from the veterans hospital population having the following characteristics: MR > 2.09 mv (upper limit plus 10 per cent); there was no evidence of infarction in the PCG; there were good clinical grounds for diagnosing pressure overload; the patients were not receiving digitalis; and the ECGs indicated only LVH. The sample thus obtained comprised 21 cases. Various PCG measurements on these 21 cases are shown in Figs. 5 and 6. Fig. 5 shows the frequency distributions of MR, tmR, QRS duration, MT/MR, and the spatial angle between R̂ and T̂—where T̂ is the maximum spatial T vector, whose spatial magnitude is MT. The distributions for MR and tmR are displaced to the right due to the basis of selection of the cases; the distribution of the QRS durations is normal. The MT/MR distribution is slightly to the left of that found for 19 veterans with normal ECGs.[a] In several cases the spatial angle between R̂ and T̂ exceeds the upper 1/2-percentile points of 149.6° and 110.6° for 184 veterans with normal ECGs and 195 young adults, respectively. This is a reflection of abnormal T vectors in these cases. Fig. 6 shows the directions of R̂, T̂, and ST̂, i.e., the vector occurring midway between the end of QRS and the T peak in the spatial magnitude tracing. The directions of R̂ are generally distributed somewhat to the left of the area of normal distribution found in a previous study of young adults (enclosed by the dashed line in Fig. 6). Since the zero meridian toward which the R̂ directions are displaced lies in the transverse or horizontal plane of the body, we see the

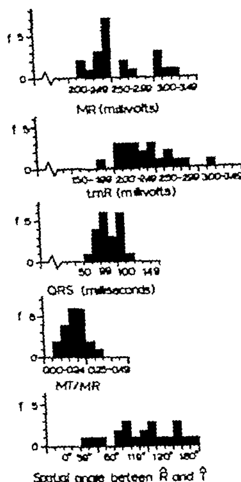


Fig. 5. PCG findings in 21 patients with uncomplicated LVH: MR (A), tmR (B), QRS durations determined from spatial magnitude tracings (C), ratios of maximum spatial T vector magnitudes MT to MR (D), and angles subtended by maximum spatial QRS and T vectors, R̂ and T̂ (E).

tendency for these cases toward a more horizontal axis. An exactly similar trend was noted for 94 subjects with MR $\geq$ 2.00 mv. reported in a previous study.[8] The directions of $\hat{T}$ may be normal—within the area enclosed by the dotted line in Fig. 6, or displaced toward the 180° meridian. The latter distribution corresponds with the T wave inversions seen in the ECG in many cases of LVH, the so-called strain pattern. The trend for $\hat{T}$ directions noted above corresponds with that reported previously for 69 subjects with MR $\geq$ 2.00 mv. *ST* directions tend to follow $\hat{T}$.

Discussion

The PCG provides in MR and tmR indices of the electric field generated by the heart for which upper limits of normal are easily defined. These limits provide PCG criteria for the diagnosis of LVH. The ECG criteria of LVH are more difficult to use because they involve several leads and are not as simply related to the heart vector. Perhaps for this reason, correlation coefficients for the various lead combinations with HW have received little or no attention. Nevertheless, the present study indicates, as one would expect, that measurements of QRS amplitudes can yield diagnoses which correspond very closely with those obtained more easily from MR or tmR measurements. The substitution of either MR or tmR for the ECG voltage measurements required for the ECG criteria employed here results in a possible reduction of the number of measurements from nine to one. This is obtained without any significant loss in the accuracy of the diagnosis. In some respects, the diagnosis might be said to be improved since the PCG diagnosis is more easily quantified for use in statistical correlation with HW or HW/BL.

The findings reported here indicate that tmR is as useful as MR in the diagnosis of LVH; indeed its coefficient of correlation with HW/BL was slightly higher (Table II). Although the difference was probably not a significant one, it might be expected that tmR would provide a slightly better index of LVH from the observation that in this condition $\hat{R}$ tends to lie more nearly in the horizontal plane—an observation in keeping with a significant, though weak, correlation between LVH and left axis

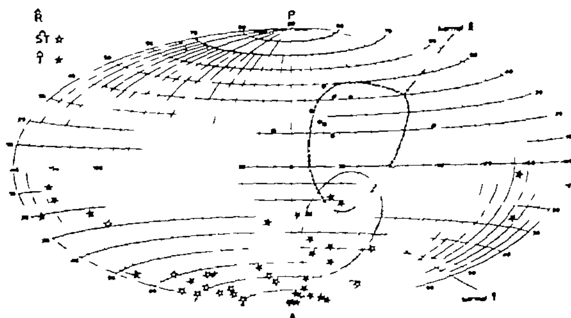


Fig. 6. Further PCG findings in same patients as in Fig. 5: directions of $\hat{R}$, $\hat{T}$ and $\hat{ST}$, i.e., the vector occurring at the mid-point in time between the end of QRS and $\hat{T}$ in the spatial magnitude tracing. The dashed and dotted lines indicate the distributions of the $\hat{R}$ and $\hat{T}$ directions found in 195 young adults from university campus.

Table II Linear regression analyses applied to 165 autopsies

Regression	*Equation*	*Correlation coefficient*
HW on MR	HW = 303.9529 + 85.5107 (MR)	= 0.4832
HW on tmR	HW = 311.6813 + 89.1394 (tmR)	= 0.4982
HW/BL on MR	HW/BL = 1.7976 + 0.4965 (MR)	= 0.4830
HW/BL on tmR	HW/BL = 1.8355 + 0.5038 (tmR)	= 0.5017

deviation. The usefulness of tmR is convenient for vectorcardiographers because it can be measured directly from the QRS loop in the transverse plane. Measurements from the transverse plane vectorcardiogram using the Frank lead system reported by Morse and associates,[14] give a normal upper 2 per cent bound of 1.64 mv. for tmR ("maximal horizontal vector") which is remarkably close to our finding of 1.68 mv. for the upper 97½-percentile in the UBC men (Table I).

The concept of LVH is a curious one and possibly a little unscientific. When a physician asks "*Does this patient have LVH?*" he is asking, in effect, whether or not the patient's heart, in response to some pathological process or condition, would weigh more at autopsy than it would have weighed if the pathological process or disease had not been present. He is therefore seeking an answer that can be provided only by an impossible experiment. Of course he can use established normal values for heart weight, but studies of HW in normal subjects show such a wide variation that a patient's HW may have increased by 50 per cent and still not exceed upper bounds for normal. Taking the body length into consideration reduces the spread somewhat, but the coefficient of correlation of HW on BL is only 0.38 for men and 0.31 for women. This means that it is not possible to make a really close estimate of what the correct HW should be from a patient's height. Other parameters may not be any better. The coefficient of correlation of HW on MR reported here was 0.48 (Table II) which is fair. An exactly similar value was recently reported by Reeve and colleagues for peak left ventricular systolic pressure vs. MR for 6 cases from which they reached the erroneous conclusion that significant correlation did not exist. However, very high coefficients for a similar correlation have been reported by Gamboa and colleagues based on 50 cases. This latter finding suggests that estimates of the usefulness of MR based on its performance in predicting heart weight at autopsy give a conservative indication of its true worth.

Conclusion

The spatial magnitude of the maximum QRS vector and the magnitude of the projection of this vector in the transverse plane provide a simple means of diagnosing LVH from the PCG. The performances of these two criteria, assessed on the basis of the PM diagnosis of LVH, prove to be about equally effective and yield results similar to those obtained by applying a certain set of voltage criteria to the ECG. They each involve a single PCG measurement, whereas the ECG criteria involve up to nine measurements.

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Inexpensive presentation of data of prolonged electrocardiographic tape recordings

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Since Holter[1] first introduced a new method for continuously monitoring the electrocardiogram in ambulatory subjects, there have been several reports confirming the usefulness of this technique in the evaluation of palpitations and syncope, in the identification of arrhythmic mechanisms, in the diagnosis of chest pain, and in the study of cardiovascular responses in a variety of physiologic and pathologic situations.[2-4] In addition, interest in continuous electrocardiographic monitoring has extended beyond the ambulatory patient into the intensive coronary care unit where much valuable information on the incidence and nature of cardiac arrhythmias has been obtained.

The most important factor limiting the widespread use of long term electrocardiographic recording is that of data reduction and analysis. We have developed a simple system of data retrieval that has distinct advantages over presently available systems. Permanent records, 4 feet in length spanning 8 hours of continuous electrocardiographic recording can be produced by a technician in 10 to 15 minutes. Abnormalities in rate, rhythm, and S-T segment contour are distinctive and readily identifiable for reproduction in standard electrocardiographic format. Transient events cannot be missed because of observer fatigue, as with the Holter Arrhythmiagraph AVSEP† technique, and the system is less expensive and more versatile than other systems.[5]

Technique

The amplified signal from magnetic tapes played at sixty times the recording speed on a Viking Model 87 tape deck is introduced into a simple high-speed cardiotachometer of our own design. The height of the sawtooth pattern thus produced is proportional to the instantaneous heart rate and is recorded on a Sanborn Model 62 Twin Beam oscilloscopic recorder to yield a record which we call a Rhythm Scan.

For the rapid analysis of alteration in the S-T segment and T waves, the original signal from one track of the magnetic tape is displayed on a Tektronic Type 561A oscil

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†AVSEP, the registered trademark abbreviation for Audio-Visual Superimposed Electrocardiogram.

loscope with a Type 3A3 time base externally triggered by the cardiotachometer signal from a second track. This display of exactly superimposed PQRST complexes is photographed with a Tektronix C12 camera base to which is attached a magazine and paper transport system built from a discarded Sanborn Twin Beam mechanism. The resultant photographic record is called an S-T Contour Scan.

These Scans are 4 feet in length and summarize 8 hours of original electrocardiographic data. Abnormalities can be spotted easily and measured down to one half millimeter corresponding to 1? seconds in real time, thus permitting rapid precise cuing of the tapes for reproduction in standard electrocardiographic format. Details of the electronic circuitry are to be published elsewhere.[15]

Examples

Examples of Scans showing typical abnormalities and their real time equivalents are shown in the following illustrations. Fig. 1 shows a Rhythm Scan (*lower block*) from a patient with the Wolff-Parkinson-White syndrome. The record displayed in this figure covers 1 hour of ECG recording. The dark bands are episodes of paroxysmal tachycardia. The upper blocks show the onset and offset of one of these paroxysms of tachycardia displayed in real time.

Fig. 2 illustrates the appearance of the Rhythm Scan in various conditions. The

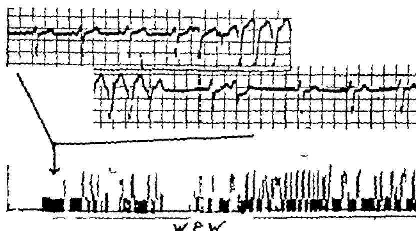


Fig. 1. Rhythm Scan from patient with W-P-W syndrome showing numerous episodes of paroxysmal tachycardia (*dark bands*). The onset and offset of one paroxysm (*arrow*) is displayed in real time.

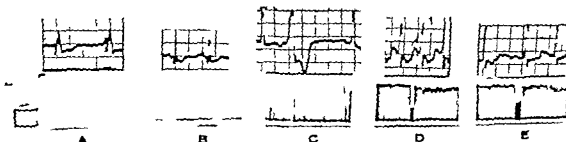


Fig. 2. Rhythm Scans showing the patterns produced by an artificial pacemaker (*A*), sinus tachycardia (*B*), ventricular extrasystoles (*C*), paroxysmal atrial tachycardia (*D*), and paroxysmal atrial fibrillation (*E*).

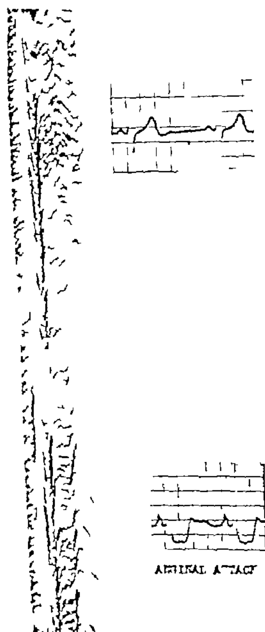


Fig. 3. S-T Contour Scan showing the rounded T waves and post T dip of a normal S-T T segment (upper portion) and the pulling away of the J point, tall peaked T waves, and loss of post T dip associated with ST-segment depression (lower portion). The QRS complex is represented by the narrow vertical band in the left-hand portion of the Scan.

first block shows the steady rhythm of an artificial pacemaker. The standardization blocks indicate rates of 100 and 200 per minute. The second block shows the smooth and gradual transition from one rate to another indicative of sinus tachycardia. Ventricular extrasystoles are illustrated in the third block. There are three zones of differing densities: the low dark bands represent the short coupling intervals of the premature beats, the middle zone the normal R-R interval, and the tall light zones, the postextrasystolic pauses. A brief episode of paroxysmal atrial tachycardia is shown in the fourth block, and the slower and less regular pattern of paroxysmal atrial fibrillation is seen in the fifth block.

Fig. 3 shows an S-T Contour Scan. There is a distinct difference in the appearance of the upper and lower portions of the scan. In the upper portion, the T waves are rounded and a prominent dip follows the T wave. This is the pattern produced by a normal ST-T segment. The lower portion shows pulling away of the "J" point, marked peaking of the T wave, and loss of the post T dip. This is the characteristic pattern of S-T-segment depression. The patterns displayed on the scan differ from the real time patterns because the electronic circuitry of the system distorts the signal into a first derivative which accentuates negative waves. However, differences from the normal pattern are easily recognized and reproduced in standard format.

Summary

Simple and inexpensive techniques for the rapid analysis of continuous electrocardiographic tape recordings are described. Permanent records, which we call the Rhythm Scan (for analysis of heart rate and rhythm) and the S-T Contour Scan (for analysis of ST-T-segment alterations) enable accurate interpretations to be made and reproduced in standard electrocardiographic format. Eight hours of continuous electrocardiographic recording can be summarized on 4 feet of paper. The Scan can be produced by a technician in less than 15 minutes.

These techniques can be applied to the analysis of continuous electrocardiographic tape recordings from patients in an intensive coronary care unit, as well as to data

obtained from ambulatory patients by the Holter technique

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An elevation of ventricular fibrillation threshold after surgical resection of infarcted myocardium

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Despite the fact that ventricular fibrillation has been a continuing challenge to medical research, the exact mechanism involved in the initiation of fibrillation is still uncertain.

We thought that quantitative measurement of the fibrillation threshold of the left ventricle might help in estimating the therapeutic value of the resection of acute ischemic myocardium.

For this reason, a study of the effects of myocardial resection on the ventricular fibrillation threshold (V.F.T.) has been carried out in experimental dogs.

Materials and methods

Adult mongrel dogs weighing from 9 to 16 kilograms were subjected to left thoracotomy and anesthetized with intravenous sodium pentobarbital. All animals were ventilated with 100 per cent oxygen by means of a mechanical respirator. It was previously reported that V.F.T. can be the same in both the unanesthetized and anesthetized animal. During the experiments the rectal temperature of the dogs was maintained constant, because V.F.T. is easily influenced by the temperature. No medication except anesthetic drugs was used.

The stimulator used to produce ventricular fibrillation was essentially the same as that used by Shumway and associates.[1] This instrument could deliver a stimulus of 8-millisecond duration to the cardiac surface at any of twelve times after the beginning of the R wave to the end of T wave. The output of the stimulator was connected to a bipolar electrode constructed of silver wires 1 cm. apart. The anodal lead to the electrode contained a 6,500-ohm resistor to minimize the effects of changing electrode resistances.

V.F.T. was determined on the anterior surface of the left ventricle in the area of distribution of the anterior descending branch of the left coronary artery, apart from the infarcted zone which was made experimentally.

Wiggers and Wegria showed that stimuli

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applied during the rise in intraventricular pressure are without effect, and that maximal vulnerability to ventricular fibrillation is in late systole a period reflected by the T wave of the electrocardiogram The final 30 to 90 milliseconds of systole is the vulnerable period Beginning with the QRS complex a single stimulus was delivered to the heart this was followed twelve times in the same way and each time the delay from the beginning of the R wave was increased After sweeping the whole cardiac cycle at one subthreshold strength the procedure was completely repeated again using a stimulus that was 2 milliamperes higher than the preceding one. This process was continued until the occurrence of ventricular fibrillation that lasted at least 3 seconds. The smallest stimulus which induced fibrillation was defined as V F T After the determination of the V F T the animals were quickly defibrillated by means of an A.C defibrillator (0 15-second duration)

Experimental dogs were divided into three groups. Determination of the V F T was performed routinely in all dogs before any other procedure was done

Group 1 (single ligation) consisted of 5 dogs The anterior descending branch of the left coronary artery was exposed at a point 1 0 cm from its origin and a ligature was passed underneath the artery for traction Two to 4 minutes after occlusion of the artery scanning was carried out. Then the occluding clamp was removed After an interval of several minutes, the coronary artery was ligated again This time scanning was started 4 to 10 minutes after the ligation. The results of this series of experiments performed in 5 dogs are shown in Fig 1

Group 2 (multiple ligation) consisted of 5 dogs. By means of ligations of the peripheral anterior descending branch of the left coronary artery several branches of the circumflex artery and a few branches from posterior descending arteries, a regional myocardial infarction was induced on the left ventricular wall including the apex, as shown in Fig 2,A The occlusions of these arteries produced a clearly demarcated myocardial infarction which was approximately 3 cm in diameter And then V F T was examined The determination was repeated in each of the dogs three times at various intervals after multiple ligation (Fig 3)

Group 3 (resection) consisted of 15 dogs. Acute myocardial infarction was produced by the same technique as in Group 2. Then in order to test the possible effects of resection of ischemic myocardium on V F T measurements were made in the same

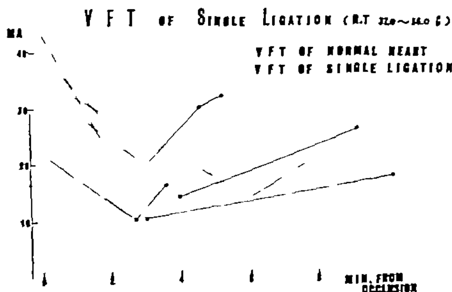


Fig. 1 V F T recovered spontaneously when a single large coronary artery was occluded.

animal before and after the myocardial resection In 10 dogs the infarction was resected surgically as completely as possible (total resection) whereas in the other 5 dogs, only the central portion of the in farcted muscle was resected (partial re-section) Five minutes after the resection, determinations of V F T were started and followed repeatedly according to the passage of time (Fig 4) After recovery of the V F T further ligation of circumflex branches was performed in all animals, and thus again decreased the V F T But the magnitude of reduction of the threshold was variable, depending upon the size of the infarct and the size of the occluded coronary arteries. This procedure was done to demonstrate that the increase in V F T after the resection was not due to the lower electrical sensitivity of the heart muscle but to the resection of ectopic focus. There were 3 dogs in which further reduc tion of V F T was not observed. These 3 were excluded from present series.

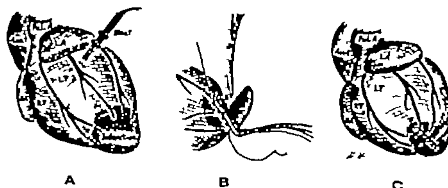


Fig 2 Partial resection of acute myocardial infarction under normothermia.

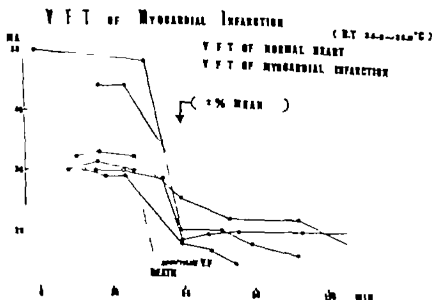


Fig. 3 V F T remained low when infarction as induced by the multiple-ligation method. One dog which died during the experiment was excluded from the statistics in the present study

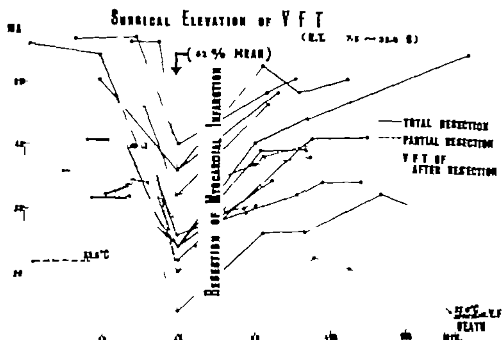


Fig. 4. Surgical resection of infarcted myocardium, which was created by the multiple-ligation method, was followed by remarkable elevation of V.F.T.

Results

Group 1. The mean pre-ligation threshold was 36 milliamperes. But the occlusion of the anterior descending branch was followed by a remarkable decrease in V F T (Fig. 1), which was most prominent for 2 to 4 minutes after the ligation. But in all 5 dogs, the V F T markedly increased as time elapsed. Especially in 4 of the 5 dogs, the V F T at 5 to 10 minutes after occlusion of the branch did not differ significantly from that obtained before the occlusion.

Group 2. The mean pre-ligation threshold was 37 milliamperes. After the formation of myocardial ischemia in all animals V F T decreased to a level varying from 18 to 30 milliamperes (mean of 22 Ma.). The mean rate of reduction was 62 per cent. During 10 to 70 minutes after the multiple ligation the decreased V F T value remained the same in 2 dogs, but it decreased slightly further in the other 3 dogs. It is assumed that both simple ligation (Group 1) and multiple ligation (Group 2) lowered the V F T and made the animals more susceptible to low levels of current. In the former method ligation was usually followed by spontaneous elevation of V F T, but in the latter method no elevation was observed after the procedure.

Group 3. Sudden occlusion of coronary arteries supplying a given area of myocardium was followed by the appearance of a rather sharply defined cyanotic area which appeared to lose its contractility. Before the procedure V F T was 44.1 ± 8.7 Ma. (±8.7 indicates standard deviation) in the 10 dogs of the total resection group and it decreased to 27.7 ± 6.9 Ma. after myocardial ischemia had been induced. In the 5 dogs of the partial-resection group V F T decreased from 34.8 to 21.4 Ma. in mean value. The reduction rate was approximately 62 per cent of pre-ligation value in both the total resection and the partial resection groups. The resection of the infarcted muscle, however, greatly increased the level of V F T both in the total resection and in the partial resection groups (Fig. 4).

The total resection elevated V F T to 42.8 ± 7.8 Ma. and partial resection to 34.5 Ma. These values after surgery are almost the same as those before ligation. V F T was progressively elevated after

resection of the ischemic myocardium except in one animal which died during the experiment.

Discussion

In the experiments in Group 1 the area supplied by the occluded artery became increasingly cyanotic and dilated. Ventricular extrasystole developed especially just after occlusion of the artery. These acute cardiac changes usually reached a stationary condition either worse or better within several minutes. V.F.T. showed the lowest value in this unstable phase. *It was quite interesting to note that the V.F.T. became increasingly elevated after it had reached the minimum value. This fact presumably indicates the rapid production of collateral circulation to the ischemic area.*

At first we had planned to observe recovery of the V.F.T. after surgical resection of ischemic muscle experimentally produced by single ligation of the anterior descending branch of the left coronary artery. But we came to prefer the multiple ligation to the single-ligation method even though the former was not followed by spontaneous elevation of V.F.T. as was the case with the single-ligation method wherein elevation of V.F.T. was usually rapid and spontaneous, as in the experiments of Group 1. It may be regrettable that previous investigators[1] used V.F.T. as a method of evaluation after ligation of a single large coronary artery without consideration of the factor of time after ligation. The value of V.F.T. remained constantly *low after the multiple-ligation method* as in Group 2. This findings shows that collateral circulation rarely developed *when the ischemic area was made by* multiple coronary ligations.

Soon after resection of the ischemic area the V.F.T. recovered to normal range. Defibrillation seemed to be easily obtained by removing the ischemic muscle. The procedure of myocardial resection was rather simple taking only several minutes. The use of *mattress and running sutures* after the excision was sufficient to prevent ventricular bleeding.

Murray demonstrated in 1947 that cardiac output was improved immediately and that the blood pressure rose after the *infarcted portion of the heart muscle was* resected. Forchers and Castellano stated that a study of the site of excision of the infarction some months *later showed a* healthy condition of the myocardium. Furukawa[1] reported that the resection of *the infarcted area was effective in prevent*ing the development of a ventricular aneurysm such as often occurred after the *onset of coronary arterial occlusion.* Usually few adverse hemodynamic effects *follow* resection of myocardium of the left heart.

Although the precise mechanism of ventricular fibrillation has not been de*fined, the circus movement theory* of Garrey[12] and the ectopic focus theory of Prinzmetal[13] are most widely accepted at the present time. *However, our findings* that V.F.T. returned to normal after resection of infarcted *myocardium* are in agreement with the ectopic *focus* theory of Prinzmetal.

It has been shown by Brofman, Leighninger and Beck that ligation of a major coronary artery or multiple ligation of all smaller arteries to a given area produces a "trigger" area which frequently leads to ventricular fibrillation (which is a break in the coordinated mechanism of the heart) and death. The relationship of current of oxygen difference and the fibrillation was expressed as the fibrillation index, that is,

$$\text{Fibrillation index} = \frac{\text{Current of oxygen difference}}{\text{Fibrillation threshold}}$$

Thus, with a high fibrillation threshold a large current is necessary to achieve the fibrillation index.

The results of our experiments in Group 3 indicate that the size of the ischemic area also seemed to be one of the important *factors to determine* V.F.T. *Partial* resection of ischemic myocardium in which there was no change in the muscular volume of the transitional zone could elevate the V.F.T. Our findings in Group 3 showed no need for resection of the transitional zone in order to elevate the V.F.T. The V.F.T. appears to be inversely related to the size of the ischemic area as well as to the severity of the ischemia.

reduction indicated by these data. The mean rise in coronary venous pressure was 1.5 mm. Hg after coronary embolization; this change, however, was not significant.

Coronary arteriovenous O_2 difference showed a small average increase after embolization but this was not significant. Myocardial O_2 uptake ($M\dot{V}_{O_2}$) fell in proportion to the reduced coronary flow. Arterial lactate concentration rose to almost double the control value after 30 minutes of shock, indicating inadequate peripheral blood flow since no significant change in pyruvate accompanied the rise in lactate. Despite an increase in arterial lactate, coronary venous lactate rose further so that the arteriovenous lactate difference fell to 17 per cent of the control value. This reduction in lactate extraction has been attributed to the presence of areas of ischemic myocardium which contribute lactate to the mixed coronary venous blood as a result of increased anaerobic metabolism.[7]

Effects of isoproterenol and norepinephrine. Infusion of isoproterenol was carried out in 14 shocked animals. The infusion was begun at a rate of 0.05 µg per kilogram per minute and increased until an increase in heart rate of 10 beats per minute occurred or until supraventricular premature beats appeared. This was achieved with a dose of 0.2 µg per kilogram per minute in most animals (range 0.1 to 0.3 µg per kilogram per minute). Ventricular arrhythmias did not appear in any animal during the infusion of isoproterenol. Infusion of norepinephrine was begun at a rate of 0.25 µg per kilogram per minute and increased until the arterial blood pressure rose to within 20 mm. Hg of the control level. The average rate of infusion was 1.0 µg per kilogram per minute (range 0.5 to 1.? µg per kilogram per minute). In 2 of 16 animals, ventricular fibrillation occurred during the infusion of norepinephrine and data from these dogs were not included. Occasional ventricular beats appeared in 2 other animals but the disturbance of rhythm was not considered to be significant to warrant exclusion of these data.

The hemodynamic and metabolic changes which occurred during the infusions of isoproterenol and norepinephrine are summarized in Table II. A comparison of the effects of the two drugs is graphically illustrated in Fig. 1. The infusion of iso-

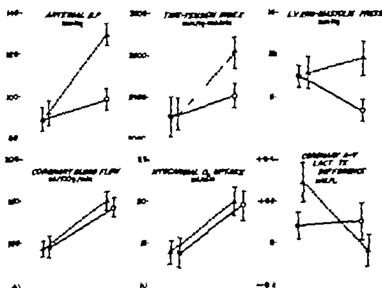


Fig. 1. Hemodynamic and metabolic changes during infusion of isoproterenol (*open circles*) and during infusion of norepinephrine (*open triangles*) in a group of dogs with cardiogenic shock. The closed symbols show the mean shock values prior to infusion of the drugs. The vertical lines and bars indicate the standard error of the mean.

Table II. Hemodynamic and metabolic effects of infusing isoproterenol (IS) and norepinephrine (NE) in dogs subjected to experimental cardiogenic shock

	A During shock		B During drug infusion				Significance between values A and B			Significance between effects of IS and NE	
	Mean	S.E.		Mean	S.E.		t	p		t	p
Blood pressure (mm. Hg)	88 5	±5 9	IS	98 8	±4 7	24	2 240	<0 05	>	5 735	< 001
	93 3	±6 2	NE	128 8	±5 0	26	6 091	<0 001			
Heart rate (beats/min.)	154 6	±7 0	IS	168 7	±7 2	24	2 732	<0 05	>	1 680	NS
	157 8	±7 5	NE	161 8	±7 5	26	1 491	NS			
Tension-time index (mm. Hg-sec./min.)	2 210	±194	IS	2 415	±116	24	1 562	NS	>	3 554	< 001
	2 237	±158	NE	2 826	±153	26	5 088	<0 001			
LV end-diastolic pressure (mm. Hg)	9 9	±1 0	IS	6 7	±1 1	24	−4 294	<0 001	>	5 628	< 001
	10 3	±1 5	NE	11 8	±1 7	26	1 796	NS			
Coronary blood flow (c.c./100 Gm./min.)	93 2	±11 6	IS	140 8	±11 9	20	3 981	<0 001	>	0 447	NS
	96 1	±8 5	NE	149 6	±10 6	24	4 604	<0 001			
Coronary vascular resistance (units)	0 89	±0 06	IS	0 70	±0 03	22	−3 125	<0 01	>	2 464	< 05
	0 99	±0 07	NE	0 90	±0 07	24	−1 047	NS			
Coronary A-V O_2 difference (vol. %)	14 70	±0 68	IS	14 01	±0 80	24	−1 664	NS	>	1 523	NS
	14 27	±0 69	NE	13 82	±0 78	24	−1 235	NS			
Myocardial O_2 uptake (mL/100 Gm./min.)	13 8	±1 9	IS	19 6	±1 8	20	4 104	<0 001	>	0 591	NS
	13 9	±1 4	NE	20 0	±1 7	22	4 799	<0 001			
Arterial lactate concentration (mM./L.)	1 109	±0 222	IS	0 960	±0 262	20	−2 075	<0 05	>	0 778	NS
	1 324	±0 294	NE	0 913	±0 160	26	−2 073	<0 05			
Coronary A-V lactate difference (mM./L.)	0 083	±0 074	IS	0 097	±0 096	20	0 101	NS	>	2 090	<0 5
	0 296	±0 128	NE	−0 036	±0 080	24	−1 856	NS			
Arterial pyruvate concentration (mM./L.)	0 117	±0 010	IS	0 100	±0 010	20	−2 852	<0 01	>	1 551	NS
	0 106	±0 017	NE	0 089	±0 014	24	−1 578	NS			
Coronary A-V pyruvate difference (mM./L.)	0 017	±0 013	IS	−0 001	±0 010	20	−2 047	NS	>	1 531	NS
	−0 010	±0 014	NE	−0 024	±0 017	20	−0 818	NS			

*See footnote to Table I

proterenol resulted in a significant increase in heart rate as was expected since this was the end point used to gauge the dosage of the drug infused. Similarly norepinephrine caused a highly significant increase in arterial blood pressure. Nevertheless isoproterenol caused a significant increase in arterial pressure in the shocked animals, whereas norepinephrine had no effect on the heart rate. Left ventricular TTI rose an average of 9 per cent with isoproterenol compared to 26 per cent with norepinephrine, a highly significant difference. The infusion of isoproterenol was accompanied by a significant fall in LVEDP (average −3.2 mm. Hg) whereas the increase in ventricular work associated with infusion of norepinephrine was associated with an average rise in LVEDP of +1.7 mm. Hg.

Although the change in left ventricular TTI was significantly different during infusion of the two drugs, isoproterenol and norepinephrine produced similar increases in coronary blood flow and $M\dot{V}_{O_2}$. Increased uptake of O_2 by the myocardium in the case of both drugs was related solely to increased coronary flow, and no significant change in coronary arteriovenous O_2 difference was noted.

In the shocked animals, prior to infusion of the drug, coronary blood flow showed a linear relationship to arterial blood pressure (R = 0.785); this is illustrated in the left hand panel of Fig. 2. Coronary vascular resistance was significantly lower during the infusion of isoproterenol than during the infusion of norepinephrine. This is illustrated in the right hand panel of Fig. 2, where the regression line for preinfusion values has been redrawn and the values during infusion of each drug have been plotted. Points representing the infusion of isoproterenol tend to fall below the original regression line indicating a lower coronary vascular resistance. Coronary venous pressure did not fluctuate more than ±2 mm. Hg during infusion of either drug, and the mean changes showed no significant difference.

Arterial concentration of lactate fell significantly during the infusion of both drugs indicating improved peripheral blood flow. Change in the extraction of lactate by the myocardium was significantly different when the effects of the two drugs

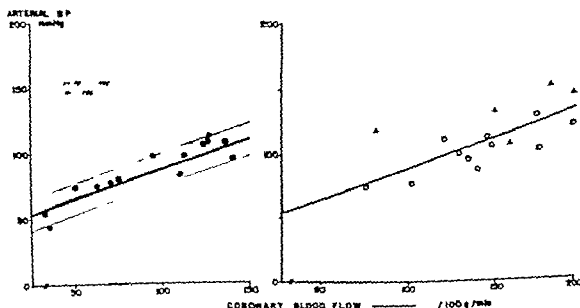


Fig. 2. *Left.* Mean aortic blood pressure plotted against coronary blood flow in a group of dogs after coronary embolization. The shaded area encloses one standard deviation from the regression line. *Right.* Arterial blood pressure plotted against coronary flow during infusion of isoproterenol (*circles*) and infusion of norepinephrine (*triangles*). The regression line for shock values prior to infusion has been extended.

were compared. Isoproterenol elicited an average increase in myocardial extraction of lactate, whereas norepinephrine resulted in a net production of lactate across the myocardium. This difference in lactate metabolism could not be accounted for by changes in pyruvate metabolism which were not significant during the infusion of either drug.

Discussion

The magnitude of the problem posed in the treatment of patients who develop shock after acute myocardial infarction is attested to by the high mortality rate associated with this complication. Restoration of an adequate distribution of arterial blood to the peripheral tissues demands an increase in ventricular work on the part of the acutely injured myocardium and may result in further compromise of ventricular function. The results of the experiments reported here suggest that, when norepinephrine is infused in a dosage sufficient to restore the arterial blood pressure toward control levels, a deleterious effect on myocardial function is observed. LVEDP rises and a net production of lactate across the myocardium is induced. These changes suggest that norepinephrine evokes an increase in myocardial work which is not met by a commensurate increase in myocardial uptake of O_2. This conclusion is supported by the data from the isoproterenol experiments in which a similar increase in M_{O_2} was observed associated with a much smaller increase in left ventricular TTI and without change in A-V extraction of lactate across the myocardium. Since coronary A-V O difference did not increase significantly during infusion of norepinephrine, it is probable that the production of lactate observed was not a result of diffuse myocardial ischemia but of increased anaerobic metabolism in marginally perfused areas of myocardium. This increased ischemia does not appear to result from a direct vasoconstrictor effect of norepinephrine since coronary vascular resistance was unchanged during infusion of norepinephrine. Stimulation of the heart with isoproterenol caused a fall in coronary vascular resistance. It is not possible to state whether this coronary vasodilation occurred secondary to increased myocardial work or whether it was due in part to stimulation of intrinsic adrenergic vasodilator mechanisms.[1] Coronary vasodilation secondary to infusion of isoproterenol may have been a factor in preventing the development of an abnormality in lactate metabolism in this group of experiments.

Sonnenblick and his co-workers have studied the oxygen wasting property of infused norepinephrine under controlled hemodynamic conditions and have suggested that this may be explained largely by an increased velocity of contraction. Sarnoff and co-workers, using a similar preparation, noted that if the dose of norepinephrine was increased above that required to produce a maximal inotropic effect, a marked increase in O consumption occurred which was unaccompanied by a further fall in LVEDP. It is of interest that the dose level at which this effect occurred in their series of experiments in which LVEDP was initially high was of the same order of magnitude as that used in our study. It is possible that in our experiments the dosage of norepinephrine employed exceeded that required for maximal inotropic effect, and it may be argued that the differences due to infusion of the two drugs were related to dosage rather than to their pharmacologic properties. Norepinephrine stimulates both alpha-adrenergic and beta-adrenergic receptors, whereas isoproterenol is a specific beta-stimulating agent. It is likely that alpha receptor sites are strongly stimulated via reflex sympathetic nervous activity evoked by the hemodynamic consequences of coronary embolization and that they are less responsive than beta receptors at a lower dose level. For this reason norepinephrine was infused in increasing dosage from 0.2 to 1.0 μg per kilogram per minute in 4 separate experiments. The results were similar in all 4 experiments; the data from one of these are illustrated in Fig. 3. In low dosage, norepinephrine caused only a slight elevation of the arterial blood pressure accompanied by increased myocardial extraction of lactate and a fall in LVEDP, changes similar to those observed with isoproterenol infusion. When the dosage of norepinephrine was increased, A-V lactate difference narrowed and finally became positive at a dose level

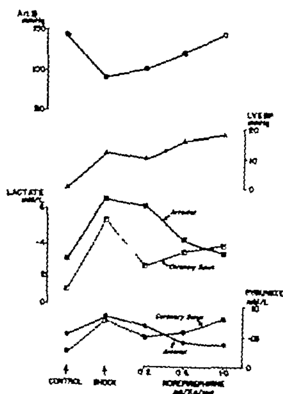


Fig. 3. Hemodynamic changes after induction of shock by coronary embolization in single animal and during infusion of norepinephrine at 3 dose levels for 15 minutes each.

of 1.0 μg per kilogram per minute. With the latter dose, LVEDP rose to above the preinfusion level in each case. Similar adverse hemodynamic responses have been observed by West and associates[19] during overtreatment with norepinephrine in coronary-embolized animals despite initial improvement at a lower dose level.

Although reports are not numerous, no such paradoxical hemodynamic observations have been reported in connection with the use of isoproterenol. Winterschied and co-workers[21] have shown a consistent relationship between increased contractility and increased $\dot{M}V_{O_2}$ in the isolated perfused heart with isoproterenol.

The results of these experiments suggest that the arterial blood pressure is misleading as a guide to regulation of norepinephrine dosage in cardiogenic shock. Intravenous norepinephrine in a dosage sufficient to evoke a satisfactory pressor response may have a deleterious effect on myocardial function. Intravenous isoproterenol in a dosage sufficient to elicit a positive chronotropic response causes inotropic stimulation of the heart but does not result in similar abnormalities of myocardial metabolism.

Summary

Cardiogenic shock was produced in 18 dogs by the technique of closed-chest coronary embolization with plastic microspheres. Isoproterenol (0.2 μg per kilogram per minute) and norepinephrine (1.0 μg per kilogram per minute) were infused for 15-minute periods into each shocked animal and the effects on myocardial function were compared.

In the dosage employed, isoproterenol and norepinephrine caused a similar increase in both coronary blood flow and myocardial O_2 consumption. Norepinephrine had a significantly greater effect than isoproterenol in raising arterial blood pressure and in increasing left ventricular work as measured by the tension time index (TTI). Increase in myocardial work was accompanied by a small increase in left ventricular end-diastolic pressure during infusion of norepinephrine, whereas isoproterenol caused a significant fall in this measurement. Both drugs decreased the level of arterial lactate, indicating improved systemic blood flow. Isoproterenol caused no change in the extraction of lactate by the heart, but norepinephrine, in contrast, resulted in the development of a negative A-V lactate difference across the myocardium with net lactate production by the heart, indicating increased anaerobic myocardial metabolism.

These data indicate that the infusion of norepinephrine may have a deleterious effect on myocardial function when used in a dosage commonly employed in treating patients with cardiogenic shock. It is suggested that isoproterenol is equally as effective as norepinephrine in improving cardiac performance after acute myocardial infarction and that its use is less likely to provoke increased myocardial hypoxia.

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Case reports

Orthostatic hypotension syndrome

A case report

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Orthostatic hypotension is often a part of a disease syndrome which includes dysfunction of other autonomic pathways.[1] Impotence, anhidrosis, and nocturnal polyuria are the most common accompanying features, but fixed pulse rate, muscular tremors, and rigidity, as well as urinary urgency, retention, and incontinence occur frequently.[1-4] The syndrome is usually secondary to a neurologic defect caused by tabes dorsalis, diabetes mellitus, or syringomyelia, but frequently the etiology is unknown and the syndrome is termed *idiopathic orthostatic hypotension*. Although the basic defect is a lack of reflex peripheral vasoconstriction in response to a fall in blood pressure, the site in the reflex arc at which the defect occurs is not known. Only 5 autopsy studies of patients with the orthostatic hypotension syndrome have been reported, and an examination of the nervous system was lacking or incomplete in 2 of these.[5-10] We recently had the opportunity to study a patient with this syndrome who later died and on whom a complete autopsy was performed.

Case report

A 43-year-old Negro male truck driver was admitted to the University of Kansas Medical Center on July 30, 1963, with the complaint of episodes of both lightheadedness and loss of consciousness over a period of 3 years. The episodes occurred while the patient was standing or sitting, but not while supine. They were never associated with convulsive movements, incontinence, or tongue biting. They occurred more frequently during the summer of admission and had become so severe that he was unable to work. He had been impotent for 6 years and had been treated for 1 year for recurrent infections of the urinary tract. Although he had been treated for hypertension in the past, he had received no hypotensive medication for 5 weeks prior to admission. Urinary frequency, urgency, and nocturia were persistent complaints, and he consistently voided larger volumes of urine during the night than during the day. His urinary stream was of large caliber and forceful. Decreased sweating had been noted for 2 years. One week prior to admission he suffered "heat stroke" and had a temperature of 105°F. He had experienced recurrent difficulty with constipation. The volume and pitch of his voice had decreased.

He had had no previous illnesses or operations and denied a history of venereal disease. A brother had died at 54 years of age of cerebral hemorrhage. There was no known family history of syncope or diabetes.

When the patient was supine, the blood pressure was 175/110 mm. Hg in the arms bilaterally. When he was seated it was 100/75 mm. Hg, but when he stood, he felt faint and his blood pressure was unobtainable. He was a well-muscled Negro man who weighed 181 pounds and was 69½ inches tall. He appeared to be younger than his stated age and in no acute distress when lying in bed. The skin was hot and dry. The pupils were equal and reacted t

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light and accommodation. The fundi revealed Grade 1 arteriosclerotic changes. The chest, heart, and abdomen were normal except for Grade 2 aortic systolic ejection murmur and systolic ejection click. The external genitalia were normal. Rectal examination revealed decreased sphincter tone and the presence of hard feces. The prostate was not enlarged. There was venous distention of the lower legs when the feet were dependent. Neurologic examination was normal. The patient was unable to cough normally but would whoop instead.

Laboratory data were as follows: Hemoglobin was 16.0 Gm. per cent with an hematocrit of 52. W.B.C. was 6,320 with normal differential; urinalysis showed pH of 5.0, specific gravity of 1.019, heavy trace of albumin, negative sugar, and 1 to 3 white blood cells per high power field. Serum electrolytes and CO_2, liver function studies, and salivary Na/K ratio were normal. The 24-hour urinary 17-ketosteroids were 13.0 mg. (normal 9 to 22 mg.) and 17-hydroxysteroids were 20.2 mg. (normal 8 to 25 mg.). 24-hour urinary vanillylmandelic acid was 4.1 mg. and 24-hour urinary catecholamines were 3 µg per cent. Total serum lipids were 653 mg. per cent and serum cholesterol was 288 mg. per cent. After 300-gram carbohydrate diet for 3 days, glucose tolerance was slightly decreased, with blood sugar (true glucose) 128 mg. per cent at the second hour. VDRL test was nonreactive. An examination of the cerebrospinal fluid was normal and urine cultures were negative. The chest x-ray film was normal except for increased bronchovascular markings in the base of the right lung. Electrocardiogram, intravenous pyelograms, skull, and kidney, ureter, and bladder x-ray films were normal.

Clinical course. In the hospital the patient had several syncopal episodes which occurred while he was standing in the x-ray department or sitting in a wheelchair. On these occasions he was noted to have very low or unobtainable blood pressure, heart rate of 85 per minute, warm, dry skin, and no nausea. Although the temperature was 101°F. on hot days, no perspiration was noted except on his face.

The blood pressure was maintained while he was walking, apparently because muscular contraction increased venous return to the heart. While he was sitting, the blood pressure was 110/80 mm. Hg, and when he was standing immediately after walking, it was 130/90 mm. Hg. Wrapping the legs to the hips was ineffective in maintaining the standing blood pressure, but this, combined with the use of an abdominal binder, elevated the sitting blood pressure and maintained the standing blood pressure for a longer period of time (5 minutes). Ephedrine was ineffective in maintaining the blood pressure, but did increase the patient's urinary urgency and frequency. While on Pro-banthine, given to alleviate the urinary side effects of ephedrine, he developed urinary retention and pyelonephritis. Panendoscopy and cystoscopy revealed no evidence of obstruction. Cystometric studies revealed a bladder capacity of 350 c.c. and a linear pressure-volume relationship which was considered normal. These studies suggested that dyssynchronous contraction of the detrusor muscle and sphincter of the bladder was a cause of functional bladder outlet obstruction.

The patient was discharged on 9-alpha fluorohydrocortisone 0.1 mg. daily, but there was no significant improvement. A Jobst counterpressure leotard, when worn by the patient, maintained the blood pressure at 90/60 mm. Hg after six minutes of standing. The Jobst suit incorporates a graded counterpressure, greater at the calf than at the thigh, to take into account the hydrostatic pressure in the blood vessels. It produces an effect similar to that of standing waist deep in water. On the tilt table in the head-up position at 30 degrees, the patient, while wearing the leotard, was able to maintain a blood pressure of 130/95 mm. Hg, whereas in the same position, without the garment, the blood pressure would become unobtainable and he would lose consciousness within 1 minute. The patient was able to return to heavy work, although he was not allowed to drive a truck. When last seen in the clinic in February, 1964, he had a tremor of both hands. On April 17, 1964, the patient died unexpectedly during sleep.

Special studies

RENAL FLOW STUDIES. The patient consistently had a larger urinary output at night than during the day. The specific gravity was usually inversely related to the urinary volume. Increased renal blood flow was indicated by a more rapid excretion of a water load when the patient was supine as well as increased clearance of phenolsulfonphthalein dye and radioactive I[131]-tagged Hippuran when he was in the supine rather than in the semi-erect position (Table I).

BLOOD VOLUME STUDIES. Decreased plasma volume was not the cause of the postural hypotension as demonstrated by the radioactive I[131]-tagged albumin technique, which showed normal values of plasma volume and no change with the patient in the supine and sitting positions (Table II).

CARDIAC OUTPUT STUDIES. Supine exercise studies demonstrated that decreased cardiac output was not the cause of the hypotension. Cardiac output was determined by the Fick principle with the patient in the supine position. The cardiac index was 2.15 L. per minute per square meter at rest with blood pressure 120/84 mm. Hg and increased normally to 3.95 L. per minute per square meter with exercise, while the blood pressure decreased to 100/70 mm. Hg.

VASCULAR REFLEX STUDIES. Incompetency of the vasoconstrictor and cardioaccelerator reflexes was indicated by the following tests. When the legs were elevated to increase venous return, the blood pressure rose from 130/90 mm. Hg to 175/110 mm. Hg. When the left arm was elevated with the patient in the supine position, the blood pressure in that arm fell from 130/90 to 100/70 mm. Hg. Carotid massage caused no change in cardiac rate, electrocardiogram, or blood pressure. When 1.0 mg. of atropine was given intravenously, no alteration in cardiac rate, electrocardiogram, or blood pressure occurred.

The Valsalva maneuver produced an abnormal response in that there was lack of hypertensive overshoot of arterial blood pressure which would normally be due to vasoconstrictor reflex (Fig. 1). There was no change in heart rate during the Valsalva maneuver, which was also indicative of the

The Jobst Institute, Inc., Toledo, Ohio.

Table I. Renal flow studies

	Supine	Head elevated 45 degrees
Water load (1,750 c.c. orally)		
Urine vol. in 1 hour	1,420	25 c.c.
Phenolsulfonphthalein I.V.		
Excretion after 45 min.	69 per cent	41 per cent
I131 Hippuran renal blood flow	534 c.c./min.	426 c.c./min.
T/2 I131 Hippuran	15 min.	27 min.

Table II. Radioactive-tagged albumin blood volume

	Blood vol. (liters)	Plasma vol. (liters)	Hematocrit
8/15/63 Supine	5.7	3.0	46.5
8/16/63 Sitting	5.4	2.8	47

absence of normal cardioaccelerator and cardiodecelerator reflexes.

The integrity of the efferent part of the reflex arc was demonstrated by a positive cold-pressor test with blood pressure rising from 80/60 to 135/95 mm. Hg within 2 minutes. Intact efferent nerve functions were also demonstrated by posterior tibial nerve block which caused vasodilatation as indicated by a rise in skin temperature in the foot from 28.5 to 36.5 degrees, and increase in digital blood flow from 1 to 75 cu. mm. per second. The fact that vasodilatation occurred indicated that vasoconstriction had previously been present, and that previously intact efferent nerve function was interrupted.

END-ORGAN RESPONSE. End-organ vasoconstrictor response was demonstrated by intra-arterial infusion of norepinephrine and of angiotensin, which caused an elevation of systemic blood pressure and a reduction in digital blood flow which was measured by venous occlusion plethysmography. Infusion of angiotensin at 10 µg per minute was followed by a decrease in digital blood flow from 30 to 5 cu. mm. per second and a rise in systolic blood pressure to over 200 mm. Hg. Infusion of norepinephrine when increased from 0.4 to 38 µg per minute led to a decrease in digital blood flow from 30 to 3 cu. mm. per second and an elevation of systolic blood pressure to 190 mm. Hg. As little as 10 milliunits of vasopressin intravenously caused a pressor response.

End-organ accelerator response was intact as demonstrated by tachycardia of 120 per minute during ephedrine administration.

The administration of pilocarpine (1/10 grain orally) was followed by sweating of the axillae as well as the forehead indicating at least partially intact sweat gland end-organ response.

Autopsy. The heart weighed 450 grams and revealed a slight left and moderate right enlargement of the cardiac chambers. Mild to moderate acute and chronic passive congestion of the abdominal and thoracic viscera was noted. There was slight vesicular emphysema of the lungs and chronic tracheobronchitis. Chronic cystitis, prostatitis, and focal pyelonephritis of the left kidney were also present.

Each adrenal gland weighed 7 grams and appeared to be grossly normal. On microscopic examination the adrenal cortex was hyperplastic with diffuse lipid depletion and some sinusoidal congestion.

The brain weighed 1,640 grams and was edematous with pale, soft parenchyma, narrowed sulci and flattened gyri. There was slight pressure coning around the cerebellar tonsils. There was no evidence of dilatation of the ventricular system. The arteries at the base of the brain were patent and showed only minimal scattered arteriosclerotic foci. The brain stem, cerebellum, spinal cord and peripheral nerves, including the thoracic sympathetic chain and ganglia, revealed no visible abnormalities. At microscopic examination it was noted that the demarcation of gray and white matter was well retained. Minute cystic foci no larger than 0.1 cm. in diameter were seen in the basal ganglia. No other abnormalities were noted.

Microscopic sections of the brain demonstrated vascular congestion with associated cerebral edema characterized by dilated perivascular and perineural spaces—the former accounting for the grossly observed status cribrosus in the basal ganglia. Occasional nerve cells had some condensation of the nuclei but no actual pyknosis. Diffuse medial calcification, not unusual for the age of the patient, was seen in many medium-sized blood vessels of the globus pallidus. The meninges were normal except for vascular changes. No abnormalities were noted in sections of the cerebellum, brain stem, or spinal cord. The sympathetic ganglionic cells and nerve fibers of the thoracic chain were well preserved and showed no significant changes.

Discussion

Our patient manifested the classical signs and symptoms of severe orthostatic hypotension syndrome as initially described by Bradbury and Eggleston. He represents one of the few reported cases of the syndrome associated with vascular hypertension.[8] Although not overtly diabetic he would have to be considered borderline or prediabetic. With symptoms of 6 years duration but without somatic sensory neuropathy or diabetic retinopathy it would not be safe to assume that this was the etiology of his illness, however.

After investigating the pathogenesis of the syndrome, Bradbury and Eggleston[1]

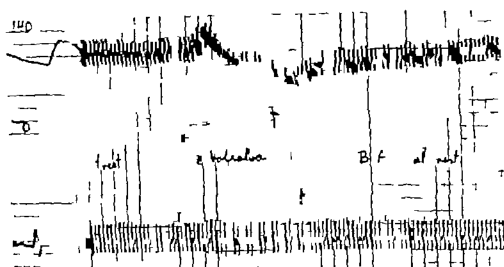


Fig. 1. Brachial artery pressure tracing made during Valsalva maneuver with patient in supine position. Units indicated are millimeters of mercury.

concluded that paralysis of the sympathetic vasoconstrictor endings seems to be the only adequate explanation of the blood pressure reactions observed in these cases. Studies of regional blood volume by Stead and Ebert[8] demonstrated that the pooling of a normal amount of blood in these patients caused an abnormal fall in blood pressure, so that the fundamental disturbance was a loss of reflex vasoconstriction in response to a fall in arterial pressure. Supine exercise studies by Marshall, Schirger, and Shepherd[11] that demonstrate a fall in arterial pressure in the presence of a normally increased cardiac output support this view. McLean, Allen, and Magath[12] utilizing the Flack[13] test (a standardized form of Valsalva maneuver) demonstrated defective return of venous blood to the heart in orthostatic hypotension and orthostatic tachycardia. Sarnoff, Hardenbergh, and Whittenberger demonstrated the usefulness of the Valsalva test as an indicator of the intactness of the sympathetic outflow, pointing out the lack of a rebound or hypertensive overshoot after administration of spinal anesthesia or tetraethyl ammonium chloride. Hickler and associates[1] found evidence of a deficient pressor amine response to tilting in postural hypotension. Hickler and associates[1] suggested that two subgroups of patients with postural hypotension could be differentiated: those with initially high and those with initially low catecholamines, the former suggesting central and the latter peripheral lesions in the reflex arc. Razavi, Nelson, and Picchi[14] found a hypersensitivity of blood pressure response to norepinephrine in orthostatic hypotension with unchanging pulse or the peripheral type. A similar phenomenon of increased sensitivity to the pressor effect of vasopressin and norepinephrine and to the depressor effect of oxytocin and nitroglycerin is found in patients who have had lumbar-dorsal sympathectomy and in patients who are being treated with ganglionic blocking agents.[14] These patients also present a clinical picture quite similar to that of patients with the orthostatic hypotension syndrome.

Postural hypotension, absence of hypertensive overshoot following Valsalva maneuver, and decreased sweating are dysfunctions of the sympathetic nervous system. Dysfunction of the parasympathetic nervous system is indicated by failure of atropine to increase cardiac rate, absence of bradycardia with use of norepinephrine and neostigmine, lack of effect of carotid massage on cardiac rate and arterial pressure, inability to obtain an erection, and absence of heart rate change with the Valsalva maneuver.[2]

The varied list of diseases found in association with the orthostatic hypotension syndrome (diabetes mellitus, tabes dorsalis, syringomyelia, encephalitis, Parkin

son's disease and basilar artery insufficiency) indicates both central and peripheral nervous system involvement.[20,21] The cases described by Thomas and Schirger[3] suggested disease of the nervous system affecting autonomic and somatic nervous structures. The site of the defect may be distinct when the syndrome is associated with specific diseases and perhaps varies in location in different cases of idiopathic orthostatic hypotension.

Stead and Ebert concluded that the site of the lesion in the reflex arc was in the sympathetic centers or their efferent tracts in the central nervous system. However, Sharpey-Schafer[20,21] has demonstrated that in orthostatic hypotension in diabetes and tabes dorsalis, stimuli arising in the brain lead to normal reactions. The performance of mental arithmetic leads to a rise in arterial pressure and hyperventilation to a fall. A single gasping breath leads to vasoconstriction in the hand, and the cold pressor test produces a rise in arterial pressure. These findings suggested to him that the efferent pathway is intact and that the afferent baroceptor mechanism is interrupted. P. B. Schneider also demonstrated a positive cold pressor test, indicating that the efferent limbs were intact. He concluded that the defect was in the afferent limb of the reflex arc. M. S. Schneider[22] described a patient with orthostatic hypotension whose orthostatic manifestations were essentially unchanged after procaine block of the right carotid sinus. He concluded that the defect should be ascribed to a lesion of the afferent part of the aortic-sinocarotid reflex mechanism.

Few autopsy studies on patients with orthostatic hypotension have been reported. Bradbury and Eggleston reported the post-mortem findings on 1 of their 3 original patients, but the brain and spinal cord were not examined. Ellis and Haynes[7] described a case in which they found cerebral edema and the brain otherwise normal except for a cyst of the left dorsal plexus. The spinal cord was not examined. Hammarström and Lindgren[8] found multiple areas of encephalomalacias throughout the brain, pons and medulla associated with multiple thrombi which were thought to be of embolic origin in a patient with verrucous endocarditis of the aortic valve. The spinal cord revealed small demyelinization centers especially in the spinal nerves, but also in the posterior roots. Drenick[9] described a patient who died in his sleep from pulmonary embolism, but the brain, spinal cord, and pituitary were normal. Shy and Drager[18] reported an autopsy in a patient with a neurological syndrome who had multiple areas of degenerative changes of neurons, particularly of medulla, cerebellum, pons, midbrain and autonomic ganglia with demyelinization of areas of the spinal cord. They described the changes as symmetrical and selective for specific systems.

The lack of significant anatomic lesions of the central and peripheral nervous systems in this patient and in the patients of Drenick and of Ellis and Haynes suggests the possibility of a metabolic or biochemical defect in the pathogenesis of the idiopathic orthostatic hypotension syndrome. Investigation of biochemical function important in transmission of the nervous impulse in the afferent limb or at the synapse between the afferent and efferent limbs of the reflex arc may prove more rewarding than have the few anatomic studies which have been done.

The sudden and unexpected death of the patient during sleep is similar to the case of Ellis and Haynes in which cerebral edema was also found. Cerebellar tonsil herniation may have been the cause of death in both cases. Drenick's patient, who also died during sleep, had pulmonary embolism.

Various modes of therapy have been utilized in patients with orthostatic hypotension.[14,24] Adrenergic drugs and fludrocortisone when administered to our patient were ineffective. Partial relief of postural hypotension was obtained with the use of elastic stockings and abdominal binder. Elevation of blood pressure when the patient was erect and relief of symptoms of postural hypotension was accomplished by the employment of a Jobst counterpressure garment.[25]

Absence of end-organ failure was established by the pressor response to norepinephrine and angiotensin. The efferent limb of the reflex arc was demonstrated to be intact by the positive cold pressor test and by vasodilatation following posterior tibial nerve block. These studies indicate that in this patient the site of the lesion in the reflex arc was in the afferent limb or at the

synapse between the afferent and efferent limbs of the reflex arc.

Summary

Physiologic and pharmacologic studies of a patient with idiopathic orthostatic hypotension syndrome suggested that the site of the lesion was in the afferent limb or at the synapse between the afferent and efferent limbs of the reflex arc. Relief of symptoms of postural hypotension was accomplished with a Jobst counterpressure garment. Post mortem examination including brain, spinal cord, thoracic sympathetic chain, and peripheral nerve revealed no significant abnormalities except cerebral edema. The lack of significant anatomic lesions of the central nervous system in this patient and in 2 other reported cases suggests the possibility of a metabolic or biochemical defect.

We wish to express our gratitude to Dr. John Kepes for reviewing the pathologic findings, and to Mrs. Maxine Fletcher for her technical assistance.

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Transient QRS changes simulating myocardial infarction associated with shock and severe metabolic stress

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The loss of electromotive force from the heart as manifested in the electrocardiogram by abnormal Q waves or change in amplitude of R and S waves, is usually considered diagnostic of myocardial infarction or at least a permanently inert area of myocardium. However, evidence from clinical and experimental studies indicates that this is not necessarily always true. The purpose of this report is to present 2 instances of QRS changes indistinguishable from those of myocardial infarction which were associated with shock and severe metabolic stress. Their transient nature and the lack of clinical features make a diagnosis of myocardial infarction extremely unlikely. Other experience from the literature and possible explanations of this phenomenon will be discussed.

Case reports

Case 1. P. R., 4-year-old white man, was admitted to the U. S. Naval Hospital, Bethesda, Md., on Feb. 10, 1960, complaining of abdominal pain, nausea, vomiting, and diarrhea. A diagnosis of enterocolitis had been established previously at this hospital when he was admitted with similar complaints in March, 1959. He had done relatively well during the previous year except for occasional episodes of mild diarrhea, cramping abdominal pain, nausea, and rare vomiting. During the month and a half prior to the current admission he had been having persistent abdominal cramping pain with frequent episodes of vomiting. Past medical history and review of systems were otherwise nonsignificant.

Physical examination on admission revealed only the findings consistent with intestinal obstruction. An abdominal x-ray film on admission supported a diagnosis of small bowel obstruction. Blood pressure was 110/68 mm. Hg.

Laboratory studies revealed: hematocrit, 29 per cent; hemoglobin, 6.8 Gm.; total protein, 4.2 Gm. with 2.7 Gm. albumin and 1.5 Gm. globulin; serum cholesterol, 88 mg. per cent; white blood count, urinalysis, and serum electrolytes, within normal limits.

Nasogastric suction was used at first, then intestinal suction with a Miller-Abbott tube, and two units of blood were administered. A series of exami nations of the small bowel with barium instilled through the Miller-Abbott tube revealed a markedly distorted mucosal pattern throughout, with marked dilatation of the jejunum, indicating obstruction. After treatment with additional blood, intravenous fluids, and 60 mg. of Meticorten daily for 4 days during the last week of February, there was sufficient improvement to remove the Miller-Abbott tube. On March 24, 1960, an exploratory laparotomy revealed a constricted segment of jejunum, 24 inches of which was resected. During the first postoperative evening, gastric distension was noted and was relieved by aspiration of 700 c.c. of air and fluid through a Levine tube. Approximately 36 hours postoperatively, the blood pressure suddenly fell to 80 systolic and the pulse rose to 120. A total of 3,000 c.c. of dextrose in water had been given. This time the patient was lethargic, but did not complain of

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pain or other discomfort. The hematocrit and serum electrolytes had been normal the day prior to surgery. At this time the hematocrit was 60 per cent, hemoglobin 18.2 Gm., serum sodium 127 mEq., chlorides 103 mEq., potassium 4.6 mEq., and CO_2 28.9 mEq. The rapid administration of 1,000 c.c. of 5 per cent glucose and saline resulted in a rise of blood pressure to 90/76 mm. Hg. Solu-Cortef, 125 mg., was given intramuscularly and another 125 mg. intravenously in a second 1,000 c.c. of 5 per cent glucose and saline as well as 10 mg. of DOCA. Physical examination at this time revealed a ventricular diastolic gallop, but no other abnormalities. The first electrocardiogram was taken at this time and showed QS in Leads II, III, aVF, V₁, V₂, and V₃ with small R waves in V₄, V₅, and V₆. The T waves were deeply inverted in all these Leads except V₁ and V₂ (Fig. 1). The following morning the hematocrit was 54 per cent, hemoglobin 16.5 gm., serum sodium 137 mEq., chlorides 102 mEq., potassium 5 mEq., and CO_2 31.4 mEq. Serum glutamic oxalo-acetic transaminase (SGOT) and lactic dehydrogenase (LDH) were normal on 3 consecutive days. Solu-Cortef was continued intramuscularly for the next 3 days and then replaced by Meticorten. The blood pressure varied between 92/70 and 104/84 mm. Hg for the next 3 days. Meticorten was finally tapered off and discontinued by April 11, 1960.

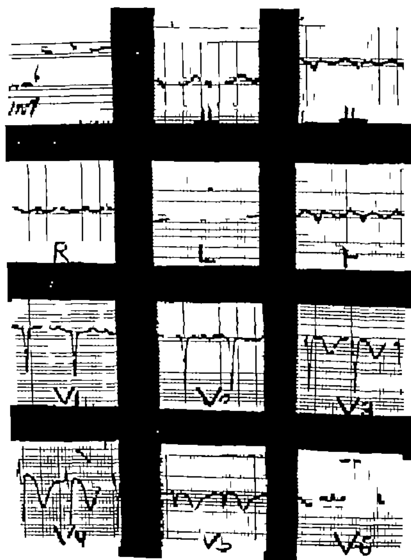


Fig. 1. Patient No. 1. Electrocardiogram at the time of the hypotension showed absence of anterior and inferior initial QRS forces which are consistent with anterodiaphragmatic myocardial infarction. T wave changes are consistent with left ventricular ischemia.

Follow-up electrocardiograms showed return of the R waves within 4 day lthough the T-w e abnormality persisted longer (Fig 2) l less tha 4 weeks the tracing was normal except for nonspecific T hanges (Fig 3) The patient graduall improved except for transient febrile period associated th right periumbilical mass which responded to penicillin and treptomycl ther pt It as discharged on M y 27 1960

Comment The shock appeared to be related to severe volume depletion possibly from gastrointestinal loss with inadequate replacement The hyponatremia and the previous short course of steroids raised the question of adrenal insufficiency but this remains uncertain.

The electrocardiogram initially was consistent with an anterodiaphragmatic infarction but the absence of pain and enzyme changes along with the rapid return of the QRS to normal in this young man are evidence against true death of tissue Ventricular dysfunction must have been present however because of the development of a ventricular gallop

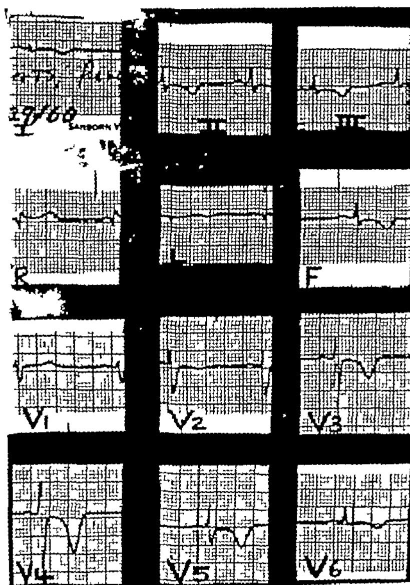


Fig 2 Patient No. 1 Four days later anterior and inferior forces had returned. The T-w e abnormality persisted.

Case 2. J. D. a 54-year-old Negro man, was admitted to the VA Hospital, Washington D. C., on May 10 1962 because of right-sided chest pain. During the prior 3 months he had developed cough anorexia, and pleuritic chest pain, with weight loss of 50 pounds. Past history revealed diagnosis of tuberculosis in 1953 and again in 1957. Similar symptoms in 1961 were diagnosed as pneumonia and he was told that the chest x-ray film had not changed from previous years. The patient had history of heavy alcoholic intake until about 8 years prior to admission. In 1954 the diagnosis of cirrhosis of the liver was made.

Physical examination revealed chronically ill Negro man with blood pressure of 110/70 mm. Hg pulse 110 per minute and temperature 102° F. He had the physical findings of a right pleural effusion and an atrial sound was heard at the lower right sternal border. Three days after admission the patient developed a supraventricular tachycardia with the rate of 200 and drop in his systolic blood pressure to 70 mm. Hg. Administration of Aramine resulted in conversion of his rhythm to sinus, and his blood pressure returned to normal levels. The electrocardiogram after conversion of the arrhythmia was unchanged from admission (Fig. 4). Attempts to wean the patient from the Aramine resulted in significant hypotension despite the addition of hydrocortisone. The patient was maintained on vasopressor agents for 12 days. The morning after the hypotensive episode, the serum sodium was 130 mEq., potassium 4.0 mEq., chlorides 89.5 mEq., CO_2 27.4 mEq., and blood urea nitrogen (BUN) 8.5 mg. per cent. On admission the sodium had been 130 mEq., potassium 5 mEq., chlorides 93.5 mEq., and CO_2 27.4 mEq. The SGOT was within normal limits

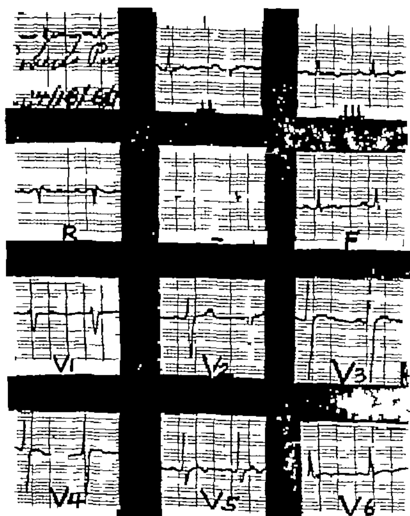


Fig. 3. Patient No. 1. Twenty-four days after the initial tracing the electrocardiogram was normal except for slight T-wave changes.

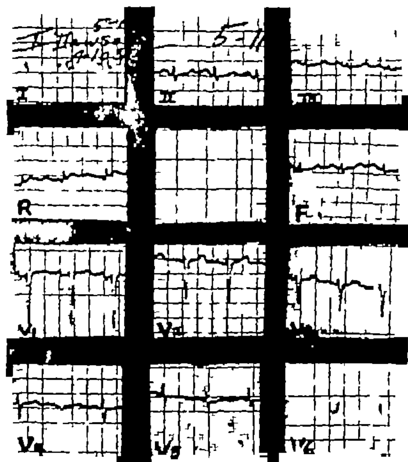


Fig. 4 Patient No. 2 Electrocardiogram th day after admission showed low voltage and nonspecific T-wave hanges but no diagnostic abnormality

for the next 2 days. An electrocardiogram taken 3 days fter the hypotensiv episode showed QS I Leads I III V V V V and small R wa es in V V and V. T es ere deeply in erted in all these leads except V (Fig 5). One day prior t this, hemodynamic tudies at the bedside with indocya nine green revealed cardiac output of 900 c. per minute and central enous pressure of 4 5 mm Hg Within 5 days, the electrocardiogram reverted back to its baseline state (Fig 6). At this time the patient was placed on digitalis. ACTH stim lation test was done for 3 day and showed no rise in urinary 17 hydroxycorticoids, which is consistent with the diag nosis of primary adrenal insufficiency The ACTH test w repeated 1 month later and revealed identi cal results. The patient as tarted on cortisone and 9-a-fluorohydrocortisone therapy nd his blood pressure was then maintained after 12 day of vasopressor therapy In addition, he was treated th isoniazid and PAS and transferred to the VA Hospital in Baltimore Md., for further treatment of his tuberculosis. At that hospital he showed gradual improvement, although he had several transient episodes of hypotension and tachycardia, but no hange in his electrocardiogram His improvement w gradual, but steady and he was finally discharged on antituberculous therapy on J uary 25 1963 The electrocardiogram t that time was within normal limits.

Comment The hypotension appeared with a supraventricular tachycardia but persisted after conversion of the arrhyth mia. ACTH stimulation tests were con sistent with adrenal insufficiency in this chronically ill patient with far-advanced tuberculosis.

The electrocardiogram though normal immediately after conversion of the ar rythmia was consistent with an acute anterodiaphragmatic myocardial infarction 5 days later The return of the electrocar diogram to normal within 5 days along with the absence of pain or enzyme changes make true death of myocardial tissue unlikely

Discussion

Abnormal Q waves are generally pathog nomonic of myocardial infarction although they may be present in instances of idio-

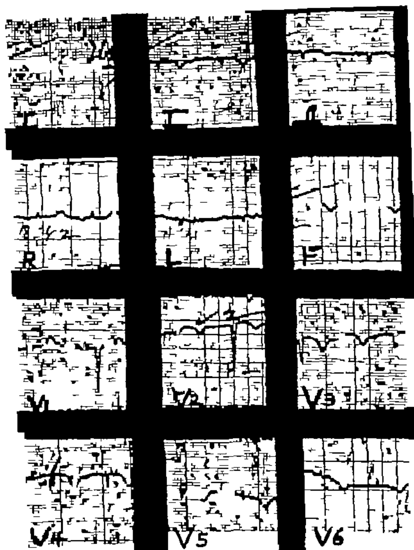


Fig 5 Patient No 2 Electrocardiogram 5 days after the onset of hypotension, showed loss of anterior and inferior initial QRS forces which are consistent with anterodiaphragmatic myocardial infarction and T-wave changes consistent with left ventricular ischemia Note the similarity with electrocardiogram in Fig 1

pathic myocardial disease, amyloid muscular dystrophy sarcoid or metastases to the myocardium Such Q waves either are permanent or resolve over a long period of time. However there have been reported instances of ischemia without infarction manifested by angina pectoris or coronary insufficiency during which Q waves have appeared only transiently Experimental production of ischemia in dogs has produced transient Q waves. Extracardiac disease has been associated with transient Q in the absence of ischemic heart disease.

Roesler and Dressler[1] reported 2 patients with typical angina pectoris who demonstrated loss of medial precordial R waves during a bout of pain In one the R waves returned immediately upon cessation of the angina in the other 2 days later T wave inversions persisted. Segers, Regnier and Delatte[2] described a patient with angina who developed a Q wave in V (during exercise) which disappeared 4 minutes later Rubin Gross and Arbeit[3] observed a patient with evidence of a healed myocardial infarction manifested by a Q in one precordial lead who on 4 separate occasions, developed widespread abnormal Q waves in frontal and horizontal plane leads during bouts of tachycardia with normal conduc

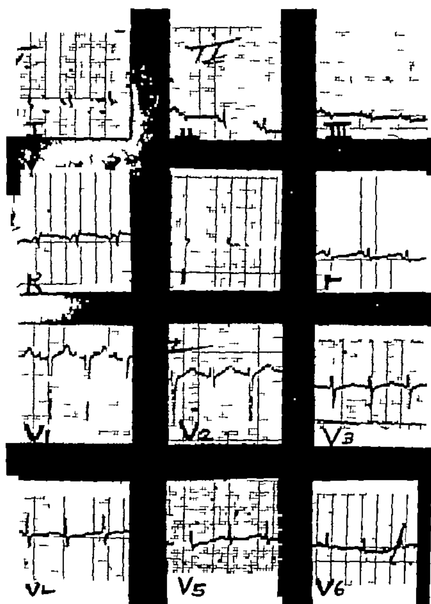


Fig 6 Patient No. 2 Five days later anterior and inferior forces have returned and the tracing is identical with the electrocardiogram during admission (Fig 4)

tion These Q waves disappeared each time with cessation of the tachycardia. Levy and Hyman observed a patient who demonstrated Q as well as ST changes diagnostic of an anterolateral myocardial infarction who showed no infarct on postmortem examination. Rubin, Cross and Vigliano[5] discussed a patient who during one of many recurring bouts of angina (relieved by nitroglycerine) showed a pathologic Q in V_2 and V_3 which was absent 12 hours later. Although there were some laboratory features suggestive of myocardial necrosis, the transient Q and lack of evolutionary electrocardiographic changes were against the presence of a transmural infarction.

Several reports of transient Q waves without infarction have been reported in the absence of apparent ischemic heart disease. Thus pancreatitis and cerebral hemorrhage have been associated with Q waves and current of injury without postmortem evidence of infarct and with minimal nonobstructive coronary atherosclerosis. Nora and Pilz[6] reported 2 patients with uremia and hyperkalemia with tran-

sient QRS, ST and T changes simulating infarction. In a case of shock secondary to an anaphylactic reaction to aspirin, Rosenfeld and associates described abnormal Q's in V and V, in a 31 year-old man which disappeared within 10 days. Goldman and associates described 3 cases which simulate ours in the common denominator of severe metabolic stress. One patient was a diabetic with carcinoma of the stomach and hypoglycemic coma, another had postoperative hypotension from blood loss, and the third had possible adrenal insufficiency secondary to prolonged steroid therapy. Each had transient Q waves in limb and precordial leads identical to our cases. Two had autopsies which demonstrated no infarct and no significant coronary artery disease.

Experimental studies have demonstrated that ischemia produced by temporary occlusion of a coronary artery in dogs may result in Q waves, without infarction which disappear when the occlusion is relieved.[11,12] Hoffman and Suckling[13] were able to reduce and restore the amplitude of the resting and or action potential of single myocardial fibers by manipulating the sodium or potassium environment. Therefore, it is evident that loss of electromotive force need not be equated with death of tissue. DePasquale, Burch and Phillips,[14] in a scholarly and complete discourse, review the concept of "electrically silent" areas of myocardium. They point out that absence of depolarization need not be synonymous with cell death. The loss of electrical activity as manifested by pathologic Q waves may reflect a temporary loss of action potential due to localized alteration in the cell membrane rather than cell death. Although electrically inactive the cell may be viable and hence regain electrical activity. It seems, therefore not unreasonable that the metabolic imbalance (engendered by the chronic debilitating illness, in our 2 patients, plus the superimposed acute hemodynamic stress) could have so altered the milieu of the cell membrane as to result in electrical silence without death of the cell.

Summary

Two patients are presented who under conditions of shock and severe metabolic stress, manifested transient Q waves in their electrocardiograms simulating myocardial infarction. The absence of clinical features and enzyme elevations as well as the transient nature of the electrocardiographic changes deny the likelihood of true infarction. Other clinical situations associated with this phenomenon are briefly reviewed and the concept of electrically silent areas of myocardium without cell death is discussed as an explanation.

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Ventricular standstill after intravenous diphenylhydantoin

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Intravenous diphenylhydantoin (Dilantin) has been advocated in the therapy of cardiac arrhythmias, especially those associated with digitalis intoxication.[1-10] To date the few untoward effects have included hypotension, bradycardia, and transient atrioventricular block.[4,5] We are reporting an instance of ventricular standstill, the apparent direct result of rapidly administered intravenous diphenylhydantoin.

Case report

An 82-year-old white man entered the emergency room of the Bronx Municipal Hospital Center with a 2-day history of breathlessness. Two months previously at another hospital he had undergone an ileotransverse colostomy because of carcinoma. Subsequently he had been maintained on digoxin, methylphenidate hydrochloride (Ritalin), and vitamins. On admission he appeared moribund. He had a regular pulse of 140 per minute, respirations of 32 per minute, blood pressure of 110/70 mm. Hg, and was afebrile. Râles were heard in the lower half of each lung field posteriorly. An electrocardiogram revealed a supraventricular tachycardia at a rate of 143 per minute with a right bundle branch block pattern (Fig. 1,A). The arrhythmia was thought to be the cause of the pulmonary congestion, and within minutes of arrival he received 250 mg. of diphenylhydantoin intravenously over a period of 2½ minutes. Continuous ECG recording disclosed the following: Within 3 minutes after onset of injection, the tachycardia had changed to normal sinus rhythm at a rate of 70 (Fig. 1,B). Seven minutes after injection the rhythm was A-V nodal at 45 per minute (Fig. 1,C), and 10 minutes after the onset of injection, cardiac arrest occurred (Fig. 1,D). External cardiac massage, intracardiac epinephrine, and sodium bicarbonate proved to be successful in resuscitating the patient. Subsequently, a hematocrit determination was reported as 15 per cent. Despite administration of whole blood and vasopressors the patient died within 3 hours of admission.

At postmortem examination† the heart weighed 500 grams and appeared to be pale and flabby. The right atrium and ventricle were not dilated and were free of thrombi. The thickness of the right ventricular wall was 0.5 cm. The left ventricle was dilated, and the left ventricular wall was 1.5 cm. thick. No evidence of myocardial infarction was present, and the coronary vessels were free of thrombi. In the right coronary artery there was a small amount of atheromatous narrowing. The lungs showed pulmonary edema, and each hemithorax contained 500 [illegible] of amber fluid. The pulmonary arteries were clear of thrombi or emboli. Histologic examination of the myocardium revealed hypertrophy of the fibers with minimal fibrosis. The colonic tumor had invaded the regional lymph nodes and pancreas.

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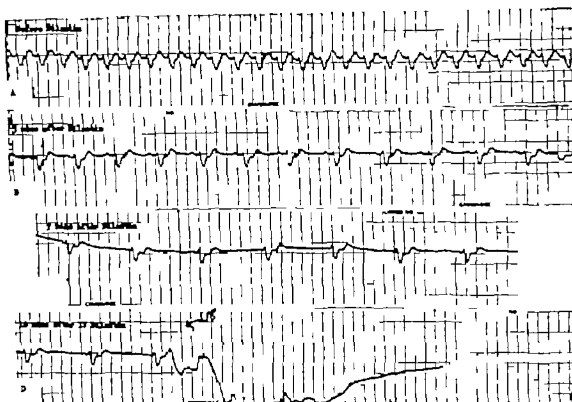


Fig. 1. All tracings are Lead II. *A*. Before administration of diphenylhydantoin. Supraventricular tachycardia at a rate of 143 per minute. Right bundle branch block. *B*. Three minutes after onset of injection. Normal sinus rhythm at a rate of 78 per minute in the first few beats. There is progressive slowing of the rate to 65 per minute at the end of the strip. *C*. Seven minutes after onset of injection. A-V nodal rhythm at a rate of 43 per minute. *D*. Ten minutes after onset of injection. Ventricular standstill.

Discussion

Although the mode of action of diphenylhydantoin on cardiac tissue is not well understood, it has been shown to depress myocardial contractility. In the dog, depression of the sinus node with subsequent asystole has been recorded.[12] Electrocardiographic changes, consisting of prolongation of the P-R interval, widening of the QRS complexes, and S-T segment and T wave changes, suggest depression of the conduction system.[13] Scherf and co-workers[14] observed a prolongation of atrioventricular conduction with development of idioventricular rhythm, severe bradycardia, and at high doses (66 to 69 mg. per kilogram) cardiac standstill. Experiments in animals have documented that rapid intravenous infusions can be lethal, but, to date, no human fatalities have been reported. In the present case there was progressive depression of the conduction system leading to cardiac arrest. We have observed one other death in a patient with advanced cardiac failure that followed rapid intravenous injection of diphenylhydantoin, but there was no ECG documentation of ventricular standstill. With slow intravenous infusion at the rate of 50 mg. per minute up to a total of 250 mg., side effects have been negligible.[10]

The drug may be used with caution in the presence of hypotension, but should be avoided in patients with slow ventricular rates or heart block because of the depressant effect on the conduction system. Presumably, severe anemia with attendant hypoxemia, as in this case, may accentuate the toxicity of any antiarrhythmic drug.

Recognition of these precautions will prevent the injudicious use of this potentially beneficial antiarrhythmic agent.

Summary

A patient who suffered a cardiac arrest after rapid intravenous injection of di phenylhydantoin is presented Slow in fusion and careful monitoring of both the electrocardiogram and the blood pressure are mandatory when diphenylhyd ntoin is employed intravenously as an ant arrhyth mic agent.

W ab t thank Dr Eph m Donoso Depart ment of Cardiology Mt Sina H spit l New York C t for his helpful m s

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Review

Plasma renin concentration in human hypertension

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Renin an enzyme of renal origin forms the pressor peptide angiotensin from a substrate present in plasma. For many years it had seemed possible that renin might normally serve to regulate the arterial pressure and also that in many forms of renal disease an excess might be released and so be responsible for associated hypertension. So far despite many claims, there has been no clear demonstration of this. A major difficulty has been due to the lack of suitably quantitative and specific methods for the measurement of the principal components of the system—renin renin-substrate and angiotensin. Pickering[24] has recently discussed some of the deficiencies of several current assay methods

In an attempt to illuminate one aspect a method was devised for the estimation of the concentration of the enzyme renin in plasma.[illegible] This technique has proved to be sufficiently sensitive to measure renin in the peripheral venous plasma of normal subjects, and in all situations encountered so far in which renin has been abnormally depressed with the exception of bilateral nephrectomy A series of patients with different forms of hypertension has been surveyed in an attempt to discern any broad outlines which would provide a basis for more detailed study [illegible]

Renin in human hypertension was analyzed in a variety of ways with reference to the etiology complications, treatment and prognosis and in relation to sodium potassium and aldosterone. The hypertensive diseases of pregnancy were analyzed separately

The present account is based on a study of renin concentration in peripheral venous plasma. Renin concentration is generally higher in renal venous plasma than in peripheral venous and arterial plasma [illegible] However the renal A V difference of renin should not be used as an index of renin secretion unless it is accompanied by simultaneous measurements of renal plasma flow [illegible]

Sodium potassium and aldosterone A highly significant inverse correlation was found between plasma sodium and renin concentration This relationship was independent of etiology of the height of the arterial pressure of complications, and of treatment. Two striking and contrasting syndromes, each with hypokalemia and increased aldosterone secretion were seen at the opposite ends of the spectrum of plasma renin and sodium concentration

Plasma renin concentration was abnormally low and plasma sodium high before treatment in primary hyperaldosteronism [illegible]

In sharp contrast there were patients

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Compressive cardiac and circulatory disorders
Clinical and laboratory correlation

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The nineteenth century brought recognition of impaired cardiac function due to cardiac compression and clinicopathologic correlation became possible. In the succeeding century the importance of certain signs emerged: venous pressure phenomena, precordial activity, gallop sounds, and respiratory variation in arterial blood pressure.[1-4] Accurate assessment of the significance of the physical signs was not always possible since, for example, postmortem evidence of fibrous constrictive pericarditis might be taken as a basis for the clinical findings of a preceding pericardial effusion. This limited the accuracy of clinicopathologic correlation.

The extensive literature on the etiology, diagnosis, and treatment of compressive cardiac disorders has been recently reviewed. Over the past decade ultrasonic, radioisotope scanning, and contrast techniques have facilitated accuracy of diagnosis. Laboratory studies have made available hemodynamic information in numerous examples of cardiac compressive disorders. Clinical correlation with pathophysiologic data has evolved which allows differentiation between cardiac compressive disorders due to structural alteration of the pericardium and mediastinal tissue, lax effusion and tamponade, as well as respiratory or extrathoracic factors which might mimic compressive cardiac disorders.

The present report has several purposes. It is intended to amplify previous reports, and to extend understanding of mechanisms by examining the effects of posture, blood volume, and venous tone on the manifestations of compressive cardiac or compressive circulatory disorders. An identification of clinicophysiologic relationships will be sought which will allow more accurate clinical recognition of various compressive circulatory disorders. Another purpose is the examination of circulatory variables as they affect hemodynamic patterns, and a further aim is the recognition of disorders which induce spurious signs of compressive cardiac disease. A final goal lies in the definition of venous compressive disease and the estimate of its possible contribution to congestive heart failure.

Methods

Selection of patients. Clinical and hemodynamic investigations were made in 68 patients.

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GROUP A There were 22 patients with constrictive pericarditis.

GROUP B Of 18 patients 9 had lax pericardial effusion and 9 had tamponade

GROUP C Of 28 patients 2 exhibited obstructive airway disease 23 had extreme obesity or tense ascites, and 3 had pericardial effusion secondary to heart failure

Clinical evaluation In previous work attention was placed on certain clinical features of compressive disease This included the level and characteristics of venous pressure and the effect of respiratory efforts on venous pressure certain auscultatory phenomena and the respiratory variation in arterial pressure

For reasons given in previous work the following definitions of certain clinical signs have proved useful (1) Kussmaul's venous sign a regular inspiratory rise in venous pressure with tranquil breathing observed in the cervical veins or recorded in the right atrium and subclavian veins (2) Friedreich's sign—an early dip in diastolic pressure observed in the cervical veins or recorded in the right atrium or superior vena cava (3) Pulsus paradoxus—palpable decrease in the strength of the pulse or a drop in systolic pressure of 10 mm or more (sphygmomanometry or direct recording) during tranquil inspiration criteria suggested by others (4) Third heart sound and pericardial knock—as per the criteria suggested by others. Timing for sound was by phonocardiogram

Diagnosis Criteria for diagnosis have been described in detail elsewhere

GROUP A Constrictive pericarditis was established by surgery or postmortem examination in 19 patients. There was extensive pericardial calcification with all other clinical signs of constrictive pericarditis in the remaining 3

GROUP B Pericardial fluid was identified by ultrasonic means, radioisotope scan angiography or pericardial tap. The diagnosis of tamponade was made when circulatory distress was evident in the presence of pericardial fluid

GROUP C. In the obese patients body weight was more than twice normal. Those with ascites had tense and protuberant abdomens.

Laboratory studies Respiratory activity measurement of right and left heart pressures and of esophageal intrapericardial and extrathoracic venous pressures were obtained by standard methods, as were estimates of cardiac output. In addition certain manipulations of the circulation were carried out in some patients in each group.

GROUP A Modification of venous pressure by venous tourniquets was performed in 8 patients, tilt to 45° from horizontal in 8 administration of ganglionic blocking agents in 5 and change in blood volume by alteration in salt and water balance or phlebotomy in 3 The effects of these measures on cardiac performance were observed

GROUP B The effect of fluid removal on cardiac index and respiratory variation in arterial pulse pressure was observed The relationship between intracardiac venous, and pericardial pressure phenomena and respiratory activity was examined once more

GROUP C In 10 of the patients who were suspected of disorders of venous return because of extreme obesity or ascites, rapid variation in venous tone (1 patient) or blood volume (9 patients) were induced (by ganglionic blockade in 1 volume expansion in 8 and phlebotomy in 1) in order to observe the effects on extrathoracic venous compression as manifested by a venous pressure gradient Notice was taken of the effects of these maneuvers on venous pressure gradient, and the effect of variation in central venous pressure on cardiac index and respiratory variation in arterial pulse pressure.

Results

Constrictive pericarditis (Group A) Table IA summarizes the clinical and laboratory findings in the 22 patients under study and Fig 1 is a representative example. There were several rather unusual responses from these 22 patients. (1) Four of the 22 patients had resting cardiac indices of more than 3.5 This was not associated with hypermetabolism tachycardia, or obvious anxiety In 2 patients elevated resting blood flow was observed on more than one study (2) An additional commentary from patients within this group was related to the occurrence of constrictive pericarditis after cardiac surgery for un

Table IA. Clinical and laboratory findings in 22 patients with constrictive pericarditis

Identification		Percentage incidence clinical findings					Hemodynamic characteristics				
							Venous pressure			Resp venous art press	Cardiac index
Age	Sex	Atrial fib	Low volt	3rd h.s. or frict. sign	Kussmaul sign	Calcification	R. ht	L. ht	(l-r)		
51	19M/3F	55	51	100	36	55	15 0	18 0	3 0 ± 0 45	10 ± 1 0	2 6 ± 0 24

Table IB The effect of venous pressure alterations in 8 patients

	High venous pressure (mm Hg)			Lower venous pressure (mm Hg)			Mean difference ± S.E.		
	Right heart	Left heart	C.I	Right heart	Left heart	C.I	Right heart	Left heart	C I
No.	8	8	8	8	7	8	8	7	8
Mean	17 6	20 4	3 4	11 5	13 4	3 8	6 1 ± 0 85	7 4 ± 0 57	0 36 ± 0 2

related disease Two of the patients had symptoms of progressive intractable heart failure 8 to 10 months after cardiac surgery for unrelated disease. One was examined post mortem less than 2 years after surgery findings included diffuse visceral pericardial fibrosis, which involved the right ventricle predominantly and associated effusion. The second patient had mitral valve replacement and because of initial improvement with deterioration 10 months after surgery he was thought to have malfunction of the mitral valve An exploration revealed thickened fibrous pericardium 2 to 4 mm in over all depth involving predominantly the ventricular chambers. This was removed the prosthetic device was found to be functioning well and the patient made a good improvement (3) Pericardial fluid concomitant with advanced visceral pericardial constriction was found in 3 patients. In the first case fluid under slight tension was noted in an 11 year-old child who had severe constriction of all cardiac chambers by fibrotic visceral pericardium This was found at postmortem examination however in retrospect it had been present for nearly 3 years. The second patient who was 57 years old died of unrecognized effusion and visceral constriction less than 2 years after surgical correction of an atrial septal defect. The large cardiac silhouette suggested myocardial disease however in retrospect, clinical signs of constrictive pericarditis were obvious. The third patient an adult with symptoms and signs of chronic pericardial disease for 4 to 5 years, exhibited angiographic features of pericardial effusion but hemodynamic features of constrictive pericarditis. It was possible to record simultaneous pressures within the intrapericardial space and the right atrium The fluid was similar to plasma and the intrapericardial pressure was several millimeters below the simultaneously recorded right atrial pressure. Subsequent surgery revealed severe visceral pericardial fibrosis with 100 to 200 ml of clear fluid between the visceral and parietal layers (Fig 1)

Venous pressure alteration The effect of venous pressure alteration in 8 patients is depicted in Table IB This maneuver was designed to evaluate [illegible]

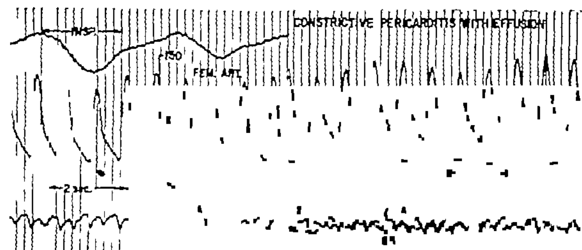


Fig 1 Con tri t perıcard t s, steral with loculated fluid in the pericardial space confirmed by rgery Left Respır t (inspir tion downward), femoral artery pressure right trial pressure Pulsus paradoxus not present Friedreich sign and descent along with Kussmaul' enous sign present Right, Recording as on left but add tion pressures recorded from needle tip placed in fluid loculation subxiphoid pproach Fl id pressur several millimeters of mercury lower than right trial pressure

Tabl II Peri ardial fluid lax effusion and tamponade

Identification		Incidence — Clinical finding				Hemodynamic haracteristics—mean ± S.E (mm Hg)			
Age	Sex	Rhythm NSR/AF	Low volt	Puls s pa	K ssmaul' sign	Rt venous pressure	Pericard pressure	Cardiac index	Δ C I fter tap
A La effusion (9 patients)									
42	4M/5F	100/0	25	22	0	9 0 ± 1 0	5 0 ± 1 5	2 8	+0 1 ± 0 2
B T mponade (9 patient)									
51	6M/3F	89/11	0	89	0	21 ± 1 0	16 4 ± 1 5	1 9	+0 48 ± 0 7

for elevated venous pressure in maintenance of cardiac output Reduction of venous pressure by venesection variation in salt and water metabolism or venodilatation resulted in a parallel drop in right and left heart filling pressures. A small increase in mean cardiac ndex was seen however this increase was not statistically significant Application of a venous tourniquet to the lower extremities or 45° tilt did not cause a significant change in venous pressure or cardiac index.

Lax effusion and tamponade (Group B) A summary of the findings in 18 patients with pericardial fluid is given in Table II and Fig 2 provides an example. Tamponade was associated with a marked pulsus paradoxus in every patient except one with severe calcific valvular aortic stenosis (Fig 3) In this instance there was ventricular pulsus paradoxus as we have previously noted The cardiac index was reduced significantly to 1 9 It tended to increase after fluid removal however in 2 of the patients, there was no significant change even though the venous and pericard al pressures could be reduced by fluid removal In all continued removal of fluid ultimately relieved the paradoxic pulse so that respiratory variation in arterial pulse pressure was less than 20 mm Hg

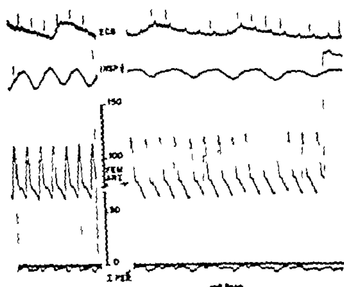


Fig 2. La pericardial effusion. Top t bottom Electrocardiogram respiration femoral artery pressure, and intrapericardial pressure Left panel Before removal of fluid. Right panel After removal of ₋50 ml of fluid. Small but regular decrease in intrapericardial pressure with inspiration before and after fluid removal Reproduced from Lange R L Circulation 33 763, 1966, by permission of the American Heart Association, Inc.

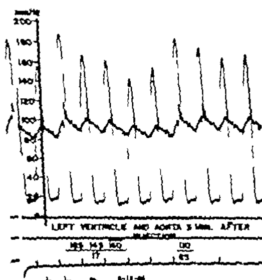


Fig 3 T mponade Severe calcific aortic stenosis. After penetration of lef entricular all by injection of contrast ma erial, pulsus paradoxus of the left entricular pressure as not reflected by equ alent changes in aortic systolic or pulse pressure. Reproduced from Lange, R L. Circulation 33 763, 1966, by permission of the American Heart Association, Inc.

Once more we confirm our previous observations that inspiration is associated w th a decrease in right and left ventricular filling pressure as well as intrapericardial pressure. Neither Friedreich s sign nor Kussmaul s sign was observed in any patient A prom nent x descent was observed before and after fluid removal in tamponade (Fig 4)

C ulatory compression by obesity and ascite (Group C) We have previously noted that extreme obesity is associated with extrathoracic venous hypertension which does not reflect central venous pressure. This is frequently associated with respiratory variation n pulse pressure that would fall w th n our criteria of pulsus paradoxus. Table IIIA ncludes findings in 15 patients with a mean weight of 138 kilograms and 8 additional patients w th tense ascites (see also Fig 5)

We have postulated that at the thoracic inlet, an abrupt d op in extramural vascular pressure occurs. Augmentation of right heart output during inspiration causes rapid depletion of a short extrathoracic segment and local collapse occurs soon after inspiration begins. Therefore the extrathoracic venous pressure does not

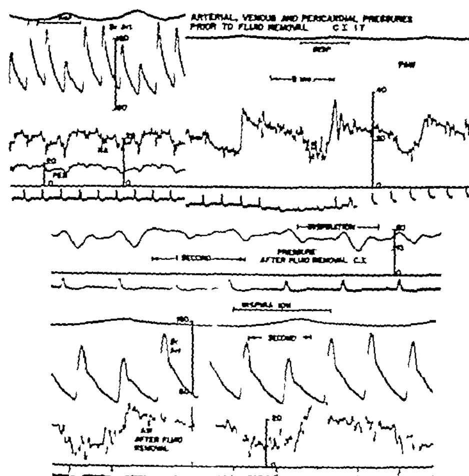


Fig. 4. P rcardial tamponade doe t m on by meta tatic t mor of pericardial space. Top panel, left: Respir tion brachial rtery pressure (pulsus paradoxus). Righ trial pressure (22 mm. Hg mean) and intrapericardial pressure (18 mm. Hg mea . Top panel, right: Respir tion pulmonary artery edge pressure (24 mm. Hg mea). Inspiratory drop is noted in enous and pericardial pressure. Middle panel: Right atrial pressure after remov l of 200 ml. of fl id; prominent descent present; mean pressure 15 mm. Hg. Lower panel: Decrease in pulsus par doxus; reduc ion in pulmonary artery edge pressure (18 mm. Hg mean).

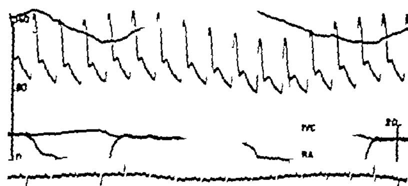


Fig. 5. Spurious igns of cardiac compression obesity. Top t bottom: Respiration (impedance method inspira tion downward), brachial artery pressure (calibration t left), inferior ena ca l and right trial pressures electrocardiogram. Time lines 1 second. Pulsus paradoxus and inspiratory IVC and RA pressure gradient are evident. Voluntary prolongation of expiratory pause left and center accompanied by rise nd f ll in arterial pressure. Reproduced from Lange, R. L. Circulation 33: 63, 1966, by permission of the American Heart Association, Inc.

reflect right atrial pressure. In general, inferior vena caval pressure tends to rise slowly during inspiration. This we have found roughly equivalent to the rise in intragastric pressure during inspiration The patients who were depicted in Table IIIA did not show any evidence of intrinsic heart disease

Table IIIB summarizes the findings in 10 patients with obesity or ascites who underwent modification of venous tone or blood volume Eight of the 10 patients exhibited evidence of inspiratory venous obstruction. In 2 additional patients extrathoracic obstructive phenomena were induced by venodilatation by tetra-ethyl ammonium chloride or after a 500 milliliter phlebotomy When the circulatory state of extrathoracic obstruction during inspiration was compared with the state of no obstruction certain effects on cardiac index, right and left filling pressure and respiratory variation in pulse pressure were noted The state of extrathoracic obstruction was associated with rather striking respiratory variation in pulse pressure and a lower mean cardiac index. When volume expansion was applied to maintain venous pressure in all portions of the circulation the extrathoracic venous pressure was only slightly higher than in the obstructed state similar relationships were seen in 2 patients in whom no obstructive phenomena were observed without phlebotomy or venodilators. On the other hand the respiratory variation in venous pressure was less striking with elimination (or decreased magnitude or duration) of the inspiratory intrathoracic extrathoracic pressure gradient. In 3 patients with ascites, a tilt to 45° angle eliminated the inspiratory obstruction at the

Table IIIA. Venous compression effects in obesity and ascites

	Identification					Hemodynamic characteristic							
	No.	Age	Sex	Wt (kg)	Body surface area (M^2)	Pulsus paradoxus	Cardiac index	Right atrium			Inferior vena cava		
								Insp	Exp	Mean	Insp	Exp	Mean
Obesity	15	45	7M/8F	138	2 47	9/15	3 0	−0 65	+12	+8	+14 3	+12 9	+13 9
Ascites	8	38	8M	80	1 89	4 8	4 0						

Table IIIB Modification by volume or venous tone (all pressures in millimeters of mercury)

	Cardiac index	Respiratory pulse press	Pulm art wedge			Right atrium			Inferior vena cava			Esophagus		
			Insp	Exp	Mean	Insp	Exp	Mean	Insp	Exp	Mean	Insp	Exp	Mean
N	10	10		6			10			10			6	
Obstruction	2 99	24 3	2 8	18 7	12 8	0 3	11 8	7 8	14 8	14 0	14 0	−14 7	13 2	−1 8
No obstruction	3 81	14 3	6 6	20 8	15 6	9 0	14 7	12 1	15 8	15 6	15 7	−15 3	10 8	−2 5
d	0 82	10 0												
S E.	0 26	2 6												

diaphragmatic level and in these patients, tilt to this position was not associated with a drop in cardiac index. Pulsus paradoxus was relieved in all patients who received volume expansion. The mean respiratory variation in arterial pulse pressure dropped from 24.3 to 11 mm Hg.

Discussion

Cardio-thoracic coupling. Whereas constrictive pericarditis and pericardial fluid have a common effect of limiting diastolic filling of the heart, it is important to consider the inelastic coupling between the heart and extracardiac structures in constrictive pericarditis, and the fluid coupling with inertial and viscous reactances in the case of effusion or tamponade. This is particularly important when the venous pressure phenomena during diastole are examined. Brecher[11] has discussed the various contributions to venous pressure phenomena. Under normal circumstances, the early diastolic forces are comprised of restorative myocardial action and the negative intrapleural pressure. These forces, which are closely coupled mechanically by normally compliant pericardium and myocardium, may not be obvious in the cervical veins because of the low venous pressure. An elevation of venous and right heart diastolic pressures in, for instance, congestive heart failure, allows emergence to clinical recognition as the early diastolic and inspiratory drop in venous pressure. It is attractive to conclude then that the uniform finding of venous pressure signs and third heart sounds in constrictive pericarditis is related to the myocardial and mediastinal coupling by fibrous structures which causes an exaggeration of restorative diastolic forces. However, since the difference between restorative forces in constrictive pericarditis and congestive heart failure is quantitative not qualitative, clinical delineation between the 2 entities is difficult on the basis of venous and auscultatory phenomena alone. It is reasonable to point out, however, that the diagnosis of constrictive pericarditis is untenable in the absence of either venous diastolic dip phenomena or third heart sounds.

On the other hand, when significant fluid is present in the pericardial space without alteration of cardiac or pericardial compliance, the retractive forces due to negative intrapleural pressure are still transmitted although imperfectly. This accounts for the decrease in pericardial pressure on inspiration previously noted.[4] The decreased intrapericardial pressure and augmented right ventricular output combine to reduce right atrial and venous pressure during inspiration. The inertial effects of pericardial fluid would have less influence on the transmission of very low frequency pressure variations of respiratory origin. However, damping of the restorative myocardial forces (which are of higher frequency) may occur because of the inertia of extracardiac fluid mass, which will prevent the formation or recognition of discernible venous pressure phenomena.

Kussmaul's venous sign was not observed in patients with pericardial fluid. We confirm the observation of Hitzig[12] and agree with his conclusion that Kussmaul's venous sign, an inspiratory rise in venous pressure, typically late in inspiration, is a common finding in constrictive pericarditis and severe cardiac failure with elevated right heart pressure. When venous pressure is elevated, there is a tendency towards transmission of the effects of increased intraabdominal pressure during late inspiration. This normal tendency towards translocation of caval blood from the abdominal cavity during late inspiration cannot be accomodated by the relatively fixed stroke output of the right heart chambers. Although we agree with Hitzig[12] and Wood[9] that Kussmaul's sign does not discriminate between constrictive pericarditis and congestive heart failure, we do suggest that when present, Kussmaul's sign may be evidence against cardiac compression by fluid.

Pulsus paradoxus. Pulsus paradoxus was described by Kussmaul before auscultatory blood pressure determinations had been devised. Our criteria were suggested by Gauchat and Katz[13] and we have extended these to include a pulse pressure variation of 20 mm Hg. Table IA indicated that respiratory variation in pulse pressure in constrictive pericarditis does not reach the magnitude which we have defined as

pulsus paradoxus. The high incidence of atrial fibrillation renders examination for this sign impossible in many patients with constrictive pericarditis.

We have previously reported that pulsus paradoxus is not present in patients who exhibited pericardial effusion incidental to congestive heart failure from acute or chronic heart disease.[4] These patients exhibited right and left ventricular dilatation at surgery or this was noted on angiocardiography. Although pulsus paradoxus was absent these patients had elevated venous pressure a prominent third heart sound and considerable cardiogenic venous pressure variation. We would conclude that the combination of primary signs of myocardial disease and the absence of pulsus paradoxus would allow the conclusion that the pericardial fluid was not responsible for the distress. Therefore fluid removal would be of little therapeutic value.

Pulsus paradoxus was uniformly present in the 9 patients with the syndrome of tamponade with one notable exception—coexistent aortic stenosis (Fig. 3). In this instance intraventricular pressures revealed the extreme respiratory variation of systolic pressure however these could not be faithfully transmitted to the arterial system because of the high degree of obstruction. Since cardiac catheterization in the investigation of aortic stenosis may require transseptal or transventricular puncture tamponade may be unrecognized since the hypotension and elevated venous pressure may not be accompanied by pulsus paradoxus.

Early work on the mechanism of pulsus paradoxus emphasized the biphasic character when inspiration was followed by a voluntary expiratory pause. The early inspiratory drop in arterial pressure and pulse pressure was promptly followed by a subsequent rise in arterial and pulse pressures even though inspiratory efforts were maintained or prolonged expiratory pauses could be carried out. The late augmentation of left ventricular output is greater in magnitude than the brief deficit during early inspiration. The time course of this biphasic phenomenon is shorter than that required for vasoconstriction and therefore, we conclude that inspiration augments cardiac function in a normal but slightly asynchronous manner.

We[4] have reported relationships between pericardial pressure venous pressure and arterial pressure in patients with airway disease. One patient had no evidence of pericardial disease and we noted that his intrapericardial pressure was considerably higher than the normal intrapleural pressure. This was related to the loss of elasticity of the lung structures. A second patient exhibited findings of lax effusion along with obstructive airway disease. Pulsus paradoxus was present in both instances and was not relieved by removal of several hundred cubic centimeters of fluid in the second case. This finding persisted after complete resolution of disease in the second case and we concluded that variation in left ventricular filling in obstructive airway disease represents increased inspiratory storage in the pulmonary bed as wide swings in intra-alveolar pressure occur induced by high resistance to air flow. The absence of pulsus paradoxus in patients with emphysema but without significant airway obstruction would suggest that loss of elasticity and of negative intrapleural pressure is not the critical abnormality.

Pulsus paradoxus was present in more than 50 per cent of the patients with extreme obesity or tense ascites. We have suggested that this may be a spurious sign of pericardial disease and further submit that it is related to the venous collapse of the thoracic inlet. This sudden reduction in venous return does not allow normal expiratory augmentation of right ventricular output. This conclusion is supported by the observation that respiratory variation in pulse pressure is related to the presence or absence of the venous collapse phenomena. As these phenomena are altered by venesection venodilatation or volume expansion the respiratory pulse pressure variation is also altered.

Determinants of cardiac performance. In constrictive pericarditis variations in blood volume or venomotor tone altered both right and left heart filling pressures. This procedure was suggested by the early work of Lyons and Burwell[14] who reported

extensive long term studies on 2 patients. We confirm the relatively constant cardiac index despite variations in right heart pressures and extend this to indicate that a proportional variation in left heart pressure is unaccompanied by a change in cardiac index. Since there was no significant variation in heart rate we conclude that stroke volume remains relatively constant and independent of wide ranges of venous pressure.

The observation of an elevated cardiac index at rest in 4 of 22 cases deserves additional comment. All patients exhibited considerable elevation of right and left heart venous pressure and they were unable to excrete a salt load in the normal manner. Two of the 4 patients were examined again after intense diuretic regimens. This caused a venous pressure reduction of approximately 40 per cent. However the elevated cardiac output did not fall. In all cases, the increased cardiac output was a reflection of reduced systemic oxygen extractions, since oxygen consumption was normal. These findings suggest that a disorder of volume control independent of cardiac output was operative. One might speculate that reduced stimuli from left atrial stretch receptors might be an important factor in the disordered control of blood volume in these patients.

The effect of pericardial fluid removal on cardiac function is also noted in Table II. Although pulsus paradoxus was relieved in every case by pericardial tap the patients with lax effusion had no change in cardiac index. In the 6 patients in whom the cardiac index was measured before and after fluid removal for relief of tamponade the cardiac index rose approximately 25 per cent.

Cardiac performance in obesity and ascites appeared somewhat dependent upon the presence or absence of extrathoracic venous collapse phenomena. The intermittent pressure gradient just outside the thoracic cavity induced a series venous resistance. Guyton[13] has suggested that venous return is affected more by a given increment in venous resistance than the same increment in arteriolar resistance. Since we note that the cardiac index was significantly higher in the absence of obstructive venous phenomena one might consider that this might contribute to the production of congestive heart failure. Certainly the increased peripheral venous pressure would tend to increase the formation of edema. The increased hepatic and renal venous pressure may alter renal function or indirectly interfere with the excretion of salt and water.

Table IV relates physical signs to clinicopathologic entities. In addition the influence of alteration of venous pressure pericardiocentesis and relief of venous collapse on clinical signs is depicted. Certain general conclusions follow from Table IV. Whenever pulsus paradoxus is present it should be considered an ominous sign until clear evidence is found against tamponade. When pulsus paradoxus is associated with circulatory distress (poor perfusion venoconstriction tachycardia tachypnea high venous pressure and hypotension) tamponade is likely. When it is due to airway obstructive disease venous pressure is normal and body perfusion is adequate. If venous pressure is elevated but circulatory distress is absent (obesity) the sign is of benign origin.

Summary

Forty patients with primary cardiac compression due to constrictive pericarditis lax effusion or cardiac tamponade were studied. An additional 28 patients were presented with spurious evidence of cardiac compression or with pericardial effusion that plays an unimportant role in the circulatory disorder. Rather stringently defined physical findings were sought which might allow discrimination between cardiac disorders. Certain procedures which alter circulatory variables were carried out. The following conclusions are drawn from the results.

1 Constrictive pericarditis is associated with venous and auscultatory phenomena which do not allow separation from other forms of heart disease causing congestive heart failure. Kussmaul's venous sign is present in less than 40 per cent an x descent is inconstant pulsus paradoxus, as classically defined is not observed. Right and left heart filling pressures do not differ greatly and when varied retain similarity

Table IV. Discriminatory clinical signs in compressive cardiac disorders

Clinical signs	Const. pericarditis high tp/low tp	Pericardial Fluid			Extracardiac disorders	
		Lax eff./tap	Tamp./tap	Myocard. dis./tap	Airway dis	Obesity & ascites vein collapse/relief of venous collapse
Kussmaul's venous sign	±/±	−/−	−/−	±/±	−	± ±
Friedreich's sign (diastolic dip)	+/+	−/−	−/−	±/±	−	−/−
Third heart sound (pericardial knock)	+/+	−/−	−/−	+/±	−	−/−
Systolic dip (x descent)	±/±	±/±	±/±	−/−	±	−/±
Venous pres. > 12	±/±	−/−	+/±	+/+	−	+ +
Pulsus paradoxus	−/−	±/−	+/−	−/−	+	+/−
Circulatory distress	+/−	−/−	+/−	±/±	−	−/−

Cardiac performance appears independent of wide ranges of venous pressure.

2. In lax pericardial effusion Kussmaul's sign and Friedreich's sign, along with third heart sounds, are not present. At times, a prominent x descent is seen in venous pressure recordings. Pulsus paradoxus is inconstant with tranquil breathing but is regularly induced by deep inspiration. There is inspiratory decrease in venous pressure and pericardial pressure. Cardiac index is normal and venous pressure is less than 12 mm. Hg. Circulatory distress is not apparent and removal of fluid from the pericardium has little effect on cardiac performance.

Tamponade induces signs of circulatory distress and is regularly characterized by pulsus paradoxus and there is frequently a prominent systolic drop in venous pressure (x descent). Friedreich's sign, a third heart sound, and Kussmaul's venous sign are absent. The venous pressure exceeds 12 mm. Hg. There is an inspiratory decrease in venous pressure and pericardial pressure. The low cardiac index is usually relieved by tap. When aortic stenosis is present, respiratory variation in left ventricular systolic pressure may not be reflected by clinical pulsus paradoxus.

3. Spurious signs of cardiac compression may be due to (1) respiratory disease, (2) severe myocardial disease and incidental effusion or (3) obesity. In the first case there is pulsus paradoxus, normal cardiac index, low venous pressure, and venous and pericardial pressure decrease with inspiration. The second group does not show pulsus paradoxus and the elevated venous pressure, diastolic dip, and third heart sounds are due to heart failure. Obesity may cause pulsus paradoxus and increased peripheral venous pressure which does not reflect central venous pressure. These findings seem related to inspiratory collapse of extrathoracic vessels, since they are influenced by changes in blood volume or venous tone.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julian Frieden

Propranolol in the treatment of angina pectoris

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New therapeutic agents for the treatment of angina pectoris have usually been received enthusiastically; propranolol and similar β-adrenergic blockading agents have been no exception. However, patients who have stable, intractable angina are frequently highly emotional individuals and symptomatic improvement is difficult to evaluate. Many subjects with angina pectoris complain of discomfort only after exercise or emotional stress and control their symptoms with rest. Nevertheless, those patients who require frequent nitroglycerine tablets, or in whom angina has been disabling, represent a major therapeutic challenge. Although drug therapy and placebo therapy are often effective for brief periods in the treatment of disabling angina, long-term results have been far less impressive. The efficacy of standard antianginal drugs is based on the supposed improvement of myocardial blood supply, although this often seems futile after one visualizes extensively occluded coronary vessels. β-adrenergic receptor blocking agents represent a new approach. Efficacy remains to be proved but, undoubtedly, will be widely tested in coming years.

Mechanism of action

The mechanisms by which propranolol might alleviate anginal discomfort are still inadequately defined. An understanding of such possible mechanisms requires knowledge of the factors which may precipitate and intensify angina.

Increased myocardial work. Anginal seizures may result from tachycardia, transient rises in blood pressure and stroke volume or bursts of ectopic beats. A clear relationship exists between these factors, which may increase cardiac work and oxygen demand.

Impaired myocardial function. Congestive failure, even when clinically occult, may intensify angina by reducing coronary flow, by lowering arterial O_2 saturation, or by other less obvious mechanisms.

Diminished coronary flow. This may result from either of the above-described factors, or may occur independently as a result of increased catecholamine liberation with consequent constriction of the coronary artery.

Increased O_2 consumption. Inordinate catecholamine-induced rises in cardiac O_2 consumption may occur with only a moder

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ate rise in myocardial work. It has been postulated that circulating and locally available catecholamines may cause severe regional myocardial hypoxia when coronary flow is impaired.

*Even though β-adrenergic receptor block*ade may be important in each of the above areas, perhaps its most important effect is prevention of tachycardia. Angina may follow tachycardia induced by emotion or exercise, a result of increased circulating and locally released catecholamines. After the administration of propranolol, inhibition of catecholamine is effected, the resting heart rate is slowed somewhat, and there is a decrease in exercise- and emotional-induced tachycardia. This cardiac slowing reduces cardiac work. Increased diastolic filling of coronary arteries may occur as diastole is prolonged. There is evidence to suggest a quinidine-like antiarrhythmic effect of propranolol. Prevention or reduction in the frequency of ectopic beats may improve myocardial efficiency and coronary flow, but also alleviates precordial discomfort by lessening awareness of the heart beat.

In addition to effects on cardiac rate and ectopic beats, propranolol may block enhanced myocardial contractility that results from stress and sympathetic stimulation. Sudden and perhaps inefficient increases in work load may be prevented. Alternative suggestions as to the mode of action of propranolol have been advanced. (1) If catecholamines do produce disproportionate myocardial O_2 consumption (O_2 wasting), β-adrenergic receptor blockade of inotropic catecholamine action will be helpful. (2) Blood pressure apparently falls in patients with moderate hypertension treated over many months, hence myocardial work load and oxygen demand are reduced. (3) Experimental studies have suggested a possible effect of propranolol in suppressing sympathetically induced coronary vasoconstriction. (4) Less likely, the topical anesthetic effects of propranolol may lessen awareness of cardiac pain. (5) There is equivocal evidence to suggest that left ventricular volume may fall in some patients; thus, greater cardiac efficiency is allowed.

Clinical studies

Some of the difficulties in evaluating antianginal agents have been discussed above. However, the evaluation of propranolol is especially difficult. Adequate *double-blind studies are not possible* because both physician and patient are often aware of cardiac slowing, particularly with exertion. Slowing of emotionally induced tachycardia will undoubtedly reassure the patient and allay anxiety. Thus, true antianginal effects will be difficult to prove.

A review of approximately 200 cases which were reported in the literature in the past 2 years revealed general agreement that symptomatic improvement occurred in over half of the subjects when adequate doses of propranolol were used. In most of these studies, the value of the drug was determined on the basis of a reduction in daily nitroglycerine consumption. Propranolol dose levels varied from 30 to 100 mg. q.i.d., with the average effective daily level approximately 160 to 280 mg. Those studies in which patients were treated with less than 120 mg. daily have shown no statistically significant improvement. Few propranolol-treated patients have been studied for more than several months; thus long-term efficacy has not been demonstrated. After the administration of parenteral propranolol, exercise tolerance apparently is increased transiently. There are reports that suggest that when β-adrenergic receptor blockade is used in conjunction with prophylactic nitroglycerine, efficacy may be enhanced. Further careful evaluation of these observations is necessary. As yet, there have been *no studies* that show objective electrocardiographic improvement after oral or parenteral propranolol therapy.

Side effects

Patients with severe angina, who often have *seriously impaired myocardial function*, must be carefully observed when propranolol therapy is instituted. Dosage must be increased gradually, as propranolol may precipitate congestive heart failure by reducing myocardial contractility and cardiac output. Excessive cardiac slowing

is a potential danger. The drug is contraindicated in patients with heart block. In addition, propranolol is contraindicated in asthmatics or patients with chronic obstructive pulmonary disease. When monoamine oxidase inhibitors or psychotropic agents have been used, 2 weeks should elapse before the treatment with propranolol begins. Careful observation is essential in patients with active allergic rhinitis and in diabetics receiving hypoglycemic agents. Minor side effects such as lightheadedness, gastrointestinal disturbances, rash, and paresthesias may occur. Although thrombocytopenia and transient serum transaminase rises have been reported, no serious biochemical or hematologic abnormalities have been detected as yet.

Summary

A new approach to the treatment of angina pectoris has been introduced which uses propranolol, a β-adrenergic receptor blockading agent. Effects are based primarily on prevention of sympathetically induced increases in cardiac work rather than on coronary vasodilatation. Initial clinical reports indicate that propranolol-treated patients may require less nitroglycerine and may have improved exercise tolerance. Long term efficacy has not been demonstrated. No evidence exists that electrocardiographic improvement has occurred, nor that there is greater longevity in anginal patients who have followed long term propranolol therapy. Further clinical information is necessary in order to determine the ultimate role of propranolol or other β-adrenergic blockading agents in the treatment of angina pectoris.

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Annotations

Pulmonary edema following cardioversion

Pulmonary edem ppare tl triggered by electrical reversion of pat t th trial fibrillation has been the subject of onsiderable comment in the recent British l era re However this complication has not been me tioned potential hazard in published res of the pr edure

I rec l nr tered 52 year old Caucasian man h udde th dev loped lurred speech and eakness of the right side of his face and of his right m H had be n told of cardiac murmu in 1948 nd had been given digitalis ince 1962 for palpitations nd dy pnea Ph sical examination and ECG ev led left entric lar h pertrophy A loud pan stolic murmur and short, low-pitched mid dia tolic rumble ere ud ble at the apex Clinical and adiogr phic evidence of mild pulmonary con gestion present The cardiac rhythm was that of trial fibrillation, w th entric lar response of 110 per min te The administration of anticoagulation th rlart as begu on the second day The neurologic signs had cleared and the patient as ambulatory and mptomatic 48 hours after admission After 3 eek of ticoagulant therapy the patient underwent lectrical reversion of his cardiac hythm during transient amnesia which was provided by 160 mg of intra enous thiamylal sodium Normal sinus h thm as promptly restored with single synchronized discharge of 200 watt-second from a Lown cardioverter The heart rate was 80 t 90 beats per minut after reversion. There was no immediat diffic lty however 9 hours fter the procedure pulmonary edema ppeared. Small amounts of bloody putum ere produced. Despite initial improvement ith customary therapy the patient condition deteriorated nd he died 39 hours after cardioversion. Sinus rhythm continued until his death. The heart rat never exceeded 120 beats per minute.

Necropsy revealed severe bilateral pulmonary edema as w ll as evidence of hronic passive congestion of the lungs Upon caref l search no pulmonary emboli or infarctions were detected. The heart eighed 750 grams and the ll of the left ventricle measured 21 mm. in thickness. The mitral valve exhibited typical deformities of healed rheumatic valvulitis it orifice was estimated to be 2.0 t 2.5 sq cm. The other heart valves were normal and the coronary arteries were remarkably free of thero sclerosis.

It seems unlikely that the pulmonary edema in this patient or in the patients reported in Britain occurred fortuitously Furthermore, gross errors in technique cannot be incriminated Excessive amount of intravenous fluids, of anesthetic agents, or of a tiarrhythmic drugs were not used I the bsence of such gross technical errors, one might suspect pulmonary coronary or cerebral emboli. Clinical and necropsy evidence of these was lacking

Resnekov and M Donald felt that direct damage t the myocardium by the electrical discharge as responsible for the pulmonary edema in t least 2 of their patients. Ikram, Nixon and Arcan disagreed. They pointed out that many patients, par ticularly those in whom sinus hythm is not restored, receive several times the electrical energy that is gi en to the patients in whom pulmonary edema has appeared. It is of note that this syndrome has accompanied the restoration of sinus rhythm in all instances so far reported. Hollman and Nicholson observed a patient in whom pulmonary edema developed after spontaneous reversion of trial fibril lation t sinus hythm. The rhythm change seemed to be the only factor which could be incriminated in their case.

Might there then be something hemodynamically detrimental about return to sinus rhythm in certain unusual patients? Resnekov and McDonald nd Bell[8] suggest that after cardioversion the left entricular output of some patient ca be increased t accommodat the improved output of the right heart only t the expense of raised left atrial and pulmonary venous pressure They point out that Broch and Müller[9] observed rises in pulmonary edge pressures of as much 10.5 to 12 mm Hg in 3 patients who were studied before nd after quinidine reversion. Rarely they conclude could this pressure rise exceed the critical level for pul monary edema. This seems more likely t occur in patients with mitral tenosis or with left entricula dysfunction.

Logan and his associates ha demonstrated that mechanical trial systole need not be restored with the return of lectrical acti tion of the tria. Indeed right trial A wa es may ppear even though none is produced in the left trium Ikram Nixon, nd Arcan[4] confirm this observation nd

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suggest that postcardioversion pulmonary edema results when the atrial "booster" is restored for the right ventricle but not for the left.

It may be premature to attribute the rare occurrence of pulmonary edema that follows cardioversion to a deleterious effect of sinus rhythm. It is intriguing, however, that a possible explanation does exist. Further observations need to be made.

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Coxsackie pericarditis

Acute benign, or nonspecific myocarditis and pericarditis are "residual" diagnoses which follow the exclusion of such traditional causes as rheumatic fever. Consideration of a viral cause is often deferred until the chance of identifying the causal agent has passed. Coxsackie B group viruses have been described as a cause of myocarditis, but the results of an observation of a large epidemic of Coxsackie B5 infection in Melbourne, Australia, during the summer of 1964-65[1] suggest that this may be a more common effect than previously suspected.

During this epidemic, Fairfield Hospital admitted 321 patients with virus meningitis and numerous patients with Bornholm disease.

From these patients with meningitis, 114 strains of Coxsackie virus Type B5 and 7 strains of Type B3 were isolated (Table I). In addition, 23 strains of Coxsackie virus Type B5 and 14 strains of Type B3 were isolated incidentally from the feces of patients with other diseases, which indicated a high carrier rate in the community at that time.

During the period of the epidemic, 14 patients with pericarditis or myocarditis were admitted. 13

Table I. Sites from which 114 strains of Coxsackie B5 virus were isolated from 321 patients with virus meningitis

Site of virus isolation	*Total number of isolations from all patients**	*Number of occasions when the site was the only source of virus*
Feces	74	37
Cerebrospinal fluid	65	14†
Throat	45	4

*Thirteen patients had the virus isolated from all 3 sources.
†In 3 patients the virus was isolated solely from the cerebrospinal fluid. The fluid was normal on microscopic examination in 1 instance and had 3 leukocytes per high power field in the other.

more were investigated at the request of other hospitals in Melbourne and numerous inquiries were received from practitioners who asked for epidemic information which explained the occurrence of myocarditis in the community. These admissions and inquiries ceased with the subsidence of the epidemic.

Of the 14 patients who were admitted, 12 were adults and 2 were infants. Ten adults between 20 and 65 years of age exhibited the classical features of myocarditis or pericarditis with radiologic evidence of cardiac enlargement and the electrocardiographic changes which are seen in this disease. The severity and duration of their illness varied considerably. In 3 patients, symptoms and signs subsided in 14 to 21 days; in the remaining 7 patients, the illness lasted from 4 to weeks.

The detection of myocarditis in the other 2 adults warrants brief description. One 35-year-old woman was admitted with meningitis. Coxsackie virus Type B5 was subsequently isolated from the cerebrospinal fluid. A routine x-ray film of her chest revealed an enlarged heart which subsided spontaneously. The incidental observation of myocarditis suggests that mild forms of myocarditis and pericarditis probably escaped detection during an epidemic of Coxsackie virus infection.

The other patient, a 65-year-old man, was admitted with suspected meningitis after an episode of diarrhea. Paroxysmal atrial tachycardia and hypotension were observed and after a severe illness which lasted 3 weeks he fully recovered. Coxsackie virus Type B5 was isolated from the cerebrospinal fluid which was normal on both microscopic and biochemical examination. This case indicates that spontaneous arrhythmias or cardiac failure may be presenting features of Coxsackie B infection.

The 2 infants, 7 and 18 months old respectively, who presented with fever, tachycardia, and dyspnea had prolonged illnesses. The diagnosis of myocarditis was made on radiologic evidence of cardiac enlargement and electrocardiographic changes.

Apart from the 2 patients from whom Coxsackie virus Type B5 was isolated from the cerebrospinal fluid, virus was not isolated from the other patients with heart damage. This appeared to be due to the slow development of symptoms and late recognition of the condition after the initial febrile illness. It is unlikely that virus will be isolated unless investigations are carried out at an early stage or pericardial fluid is obtained.

Ten patients were studied serologically. Convincing evidence of recent Coxsackie virus Type B5 infection was obtained in two of them. In others, varying low titers to several of the Coxsackie B group of viruses were present and in one patient there were significant rises to 2 different Coxsackie B viruses. Difficulty in specific interpretation of these results was expected. It was emphasized at the World Health Organization meeting (Copenhagen, 1965) that certain enteroviruses may recall antibodies to other members of the same group and occasionally to heterologous enterovirus groups.

The association of these cases with an epidemic of Coxsackie B infection was most suggestive of a causal relationship. Indeed it seems that a diagnosis of Coxsackie B pericarditis or myocarditis may often depend on epidemiologic evidence in association with proof of a compatible clinical syndrome which is obtained in only a proportion of cases.

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Regulation of plasma volume

Under most conditions the circulating plasma volume is maintained within remarkably narrow limits and recovers rapidly from imposed alterations. The search for physiologic regulatory mechanisms to account for these adjustments has uncovered some but probably not all, of the details.

The restoration of volume was explained by Starling[1] as a simple transfer of ultrafiltrate between the vascular and interstitial compartments in response to purely physical factors. That such mechanism can operate with great rapidity has been frequently confirmed (e.g., Stauffer and Hyman[2]). Careful experiments have shown how precisely alterations in transmural hydrostatic pressure in the filtration area or changes in effective oncotic pressure modify the rate and distribution of extracellular fluid. However, to effect such changes in pressure in behalf of the regulation of blood volume, the balance between the needs of local tissue and the precisely metered flow of nutritional blood[3] must be

sacrificed. Although such a disparity might be tolerated for a short time, it would be incompatible with circulatory efficiency for any prolonged period. Hence it is theoretically desirable that long-range readjustments of the circulating volume be made by mechanisms that do not arbitrarily restrict the fundamental *nutritional function* of the microcirculation. Readjustments of the circulating plasma protein mass to maintain the plasma iso-oncotic during adjustment of volume offers such an alternative system. Experimental data indicate that the oncotic pressure, though subject to short-term shifts, does *in fact maintain* a relatively constant level.

Plasma protein may be pictured as traveling in at least 3 *circulations*[illegible] (1) the obvious circuit within the vascular system (2) into a rapidly exchanging circuit, including escape across the blood-parenchymal *barrier into* a compartment in which degradation of albumin probably occurs and (3) into a more slowly exchanging compartment, the function *of which is unknown*. The latter two circuits may be a statistical construct with many pool sizes in each, and with the distinguishing feature of having rate *constants* of exchange with the intravascular system which fall into two distinct groups one with a half time of several hours and the other with a half time of several days.

Ultimately regulation of the total *protein pool* depends on the balance between the rates of protein *synthesis* and degradation, but the time involved in modification of these normally *slow processes* limits their usefulness as factors for adjusting plasma volume. Apparently concentration of intravascular albumin alone does not determine the *rate of albumin synthesis*. Despite the fact that infusion of dex*trans* expands the albumin space and lowers the concentration of serum albumin in the rabbit, the synthesis of this protein diminishes.[illegible] Administration of *cortisone* to these rabbits caused an increase in plasma volume and an even *greater increase in* albumin space. These changes are accompanied by a decrease in extravascular oncotic pressure, an unequivocal increase in albumin degradation, *and an* even more marked increase in albumin synthesis.

With gradual induction of hyperglobulinemia, normal plasma volume is *maintained but the total* albumin pool size decreases with decreased degradation *of albumin* and an even greater decrease in albumin synthesis. On the other hand with abruptly induced hyperglobulinemia (as by a marked anamnestic *response*) albumin synthesis cannot shut off fast enough to prevent a rise in plasma volume. Thus, under some conditions, albumin synthesis appears to be *controlled* by extravascular oncotic levels; degradation as well as synthesis of albumin may be modified to maintain oncotic pressure. The body responds to the externally produced hyperalbuminemia after repeated injections of *intravenous* albumin by markedly increasing albumin degradation rather than *by shutting off* albumin synthesis as is the case with infusions of dextran. The site of such increased degradation might be the reticuloendothelial *system or the* gastrointestinal tract.

The low total production of each of the immunoglobulins in grams per day as compared with albumin[illegible] makes it seem likely that the immunoglobulins cannot function easily in regulating oncotic pressure.

Maintenance of a stable circulating protein mass would be better served by a *mechanism which could* regulate the transfer of protein between the vascular and the interstitial compartments. Moving protein in or out of the *vascular system to change the* circulating protein mass would permit adjustment of the circulating plasma volume at a normal oncotic pressure. *Conceivably* the *intravascular* protein mass might be altered by changes in either the rate at which protein returns to the circulation or the *rate at which it escapes* across the capillaries. Return of protein to the vascular system is almost *completely* by the lymphatic vessels.[illegible] Under most *conditions*, the rate of lymph flow is determined by factors which usually reflect noncirculatory *functions* of the body. Certainly activity of skeletal muscle profoundly modifies lymph flow[illegible] although it may be unrelated to an *over-all cardiovascular* adjustment. Similarly the increase in lymph flow in the postprandial period does not necessarily relate to the needs of the circulation.[illegible] This conflict of interests tends to rule out adjustment of lymphatic return as the regulatory system we seek.

Some years ago Hyman *and Paldino*[illegible] showed that the rate at which labelled protein (and, by implication, native protein) escaped from the active circulation could be rapidly and significantly altered by stimulation or inhibition of the reticuloendothelial system.[illegible] The responsiveness of this protein leak to a variety of pharmacologic and humoral agents recommends it as a convenient, potential efferent arm of a proposed reflex for regulating plasma proteins. The afferent *arm is not yet clearly* understood but it might be related to the sensor of oncotic pressure as suggested by Rothschild and associates.[illegible] Alternatively some *system* capable of detecting changes in the fullness of the circulatory tree *might* prove to be involved. The rapidly accumulating evidence for such a volume-sensing system in the low-pressure portion of the cardiovascular system[illegible] offers a promising area for further investigation.

We do not claim that the details of these regulatory mechanisms have been established. We merely call attention to the desirability of such a reflex and invite investigators to initiate experimental *tests of* the validity of our suggestions.

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Electrocardiographic changes typical for central nervous system disease after right radical neck dissection

The triking electrocardiographic abnormalities that occur after certa central nervous system disturbances (such as aneurysm of circle of Willis, certain types of brain hemorrhage thrombosis or tumor)[1] have gained general recognition. In contrast the mechanisms underlying the alterations in the Q-T time S-T segment and T-wa configuration ha remained matter of conjecture

Experimental evidence[2,3] ha indicated that stimulation of discrete hypothalamic areas will cause similar Q-T S-T and T-w changes and that these alterations may be abolished by C spinal cord section. Cropp and Manning[4] suggested, after they observed ECG hanges during manipulation of the circle of Willis in a patient, that the cerebral area representing the vagus (area 13) may be the origin of the pathway by which these hanges are transmitted. Working on the other end of this possible link, Barger nd co-workers[5] showed that local infusions of norepinephrine in the coronary essels caused the typical ECG changes ithout chemical evidence of necrosis.

Recentl Yanowitz and co-workers showed further that either left stellate ganglion timulation or

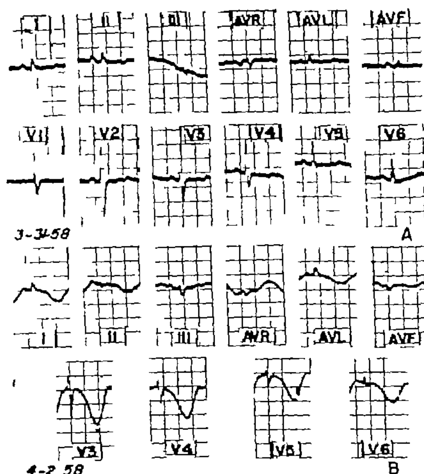


Fig. 1 *A* and *B*. A 56-year-old woman with carcinoma of the tongue. *A*, Tracing taken on 3-31-58, two days prior to operation showing flat T waves in standard and precordial leads. *B*, Tracing taken on 4-2-58 showing deeply inverted T waves, Q-T interval prolongation, and normal serum potassium and calcium levels.

right stellate ganglionectomy may give similar changes in the T wave and ST-T segment. In an extensive experimental study in dogs, they showed that such alterations were due to changes in sympathetic tone which lead to a shift in relative duration of repolarization. The patient to be described may represent the first reported clinical example of such ECG changes after surgical right stellate ganglionectomy.

A 56-year-old woman had extensive carcinoma of the tongue which invaded surrounding structures in the neck. Six hours after hemiglossectomy and radical lymph-node dissection of the entire right neck region was performed the tracing shown in Fig. 1 was obtained. It showed low voltage of the QRS complex compared to the control tracing obtained preoperatively (Fig. 1,*A*), marked S-T segment depression with Q-T interval prolongation, and rounded deeply inverted and prolonged T waves (Fig. 1,*B*). During the operation, the blood pressure decreased abruptly from 122/90 to 80/60 mm. Hg and persisted at these levels for 3 days after the procedure although the patient had no large blood loss or signs of shock. During the dissection, the carotid artery was extensively manipulated and surrounding lymph tissue dissected, but the vessel was not ligated. The patient re-entered the hospital 2 months after discharge and died with diffuse metastatic carcinoma. No autopsy was permitted.

As is frequently the case, the initial ECG interpretation was that of subendocardial myocardial infarction. However, the absence of any rise in serum enzymes, the lack of any cardiovascular symptoms or findings, the normal heart size, and the absence of any history referable to the cardiovascular system made this less likely, particularly since the ECG changes showed little alteration over the ensuing days.

In view of our experience with similar cases, the

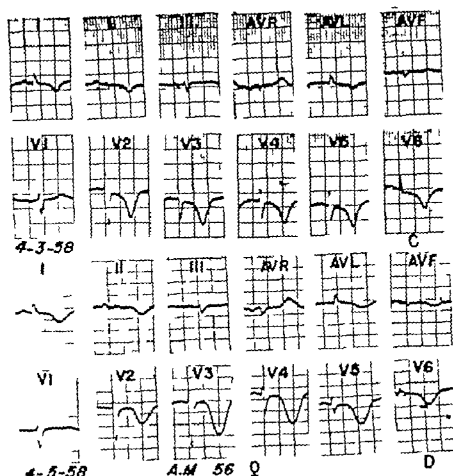


Fig. 1. C and D. C, Tracing essentially unchanged on 4-3-58 after correction of sodium and chloride deficit. D, Persistence of Q-T interval prolongation and deeply inverted T waves on 4-5-58 in the presence of elevated serum potassium level.

possibility of a primary relationship with the central nervous system was considered. The radical neck dissection with interference of the sympathetic system and the extensive manipulation of the carotid artery with the destruction of the sympathetic nerve fibers were now seen as possible causes for the sudden and persistent hypotension and for the dramatic and unchanging electrocardiographic alterations in this patient. Since these changes are identical to those observed by Yanowitz and coworkers after experimental right stellate ganglionectomy, the findings in this patient may represent the first clinical confirmation of the experimental data. Finally, this case report may forge yet another link in the chain of central nervous system abnormalities which may result in the electrocardiographic changes so characteristically demonstrated (Fig. 1, A, B, C, and D).

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Announcements

A Graduate Course in Medical Hypnosis is being offered to physicians and dentists by the University of Pennsylvania Graduate Division School of Medicine. There will be 20 4-hour weekly afternoon sessions for a total of 80 hours beginning September 28, 196[illegible]. The course will be given at the Institute of the Pennsylvania Hospital, 111 North 49th Street, Philadelphia, Pennsylvania 19139. For further information write to Sydney E. Pulver, M.D., 111 N. 49th Street, Philadelphia, Pennsylvania 19139.

A Conference on Quantitative Exercise Electrocardiography [illegible] Ernst Simonson Day will be held at the University of Minnesota Medical Center on September 28-29, 1967. Information is available from Henry Blackburn, M.D., Stadium Gate 27, University of Minnesota, Minneapolis, 55455.

A Graduate Course in Office Psychiatry is being offered to physicians by the Institute of the Pennsylvania Hospital. The course is designed to give the maximum of clinically useful information to the practicing physician who is interested in improving his ability to manage the psychiatric problems commonly encountered in the practice of medicine. In keeping with its emphasis on practical useable information, theoretical material will be kept at a minimum. The course will consist of twelve four-hour weekly sessions beginning September 28, 1967. For further information write to Sydney E. Pulver, M.D., 111 N. 49th Street, Philadelphia, Pa. 19139.

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Editorial

Safer surgery for patients with pheochromocytomas

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Pheochromocytomas are a minor cause of hypertension which account on admittedly unreliable estimates for about one half per cent of the hypertensive population. However, hypertension is such a common disease that this one half per cent is important, since the disease is completely curable by operative removal of the tumor. Before the introduction of adrenergic blocking agents the mortality rate for planned operative removal of a pheochromocytoma was 25 per cent, whereas when one of these tumors was unexpectedly present in patients operated on for other reasons, the mortality rate was 50 per cent. The causes of death were hypertensive crises after induction of anesthesia and during dissection of the tumor, hypotension following its removal, and arrhythmias resulting from sensitization of the myocardium by the use of hydrocarbon anesthetics in the presence of large quantities of circulating catecholamines.

The hazards of operation on patients with pheochromocytoma have been greatly reduced by advances in the understanding of the physiology and pharmacology of the sympathetic nervous system in the past 20 years, typified by the concept of α- and β-adrenergic receptors which were advanced by Ahlquist to explain the varying effects of epinephrine and norepinephrine on different tissues. Of major importance was the recognition that α-receptors mediated vasoconstriction of all vascular beds, particularly skin, which is characteristic of the effect of norepinephrine, whereas β-receptors mediated vasodilatation of all vascular beds, particularly skeletal muscle, but were also responsible for the chronotropic and isotropic effects of epinephrine on the myocardium.

These ideas led to the search for specific antagonists of the effects of epinephrine and norepinephrine on α- and β-receptors. The successful development of these blocking agents has had important clinical application in the preoperative and operative management of patients with pheochromocytoma by permitting for the first time pharmacologic control of both blood pressure and pulse rate and by offering protection from induced arrhythmias.

Variation of blood pressure during an operation can be controlled by the use of α-adrenergic blocking agents, two of which have been widely used for this purpose. The duration of action of phentolamine (Rogitine) is too short for its effective use during operation, but phe-

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noxybenzamine (Dibenzyline) with its longer period of action has proved much more effective for this purpose. It can and should be used to control the blood pressure of patients with pheochromocytoma in the interval between diagnosis and operation. For this purpose an oral dose of 10 mg. t.d.s. or such an amount that adequately controls the blood pressure is given. These tumors result in malignant hypertension in about 20 per cent of cases and sudden death from cerebral hemorrhage or myocardial infarction is not uncommon. The reduction of blood pressure by the use of phenoxybenzamine as soon as the diagnosis is established may be lifesaving.

Another effect of prolonged exposure to high circulating levels of epinephrine and norepinephrine is a reduction of plasma volume secondary to constriction of small vessels. Hypovolemia has been found in patients with pheochromocytoma[2] and is an important factor which contributes to the hypotension that follows removal of the tumor. The administration of phenoxybenzamine before the operation will permit re-expansion of the circulation and eliminate the necessity of postoperative infusions of norepinephrine. For this purpose it is given intravenously since full vasodilatation is rarely achieved by oral administration.

α Adrenergic blockade leaves the β-receptors exposed to the chronotropic effects of catecholamines and converts the familiar bradycardia of norepinephrine into a response which resembles that of epinephrine. The resulting tachycardia can be alarming, particularly if atropine has been given for premedication. The administration of a β-receptor blocking agent such as propranolol (Inderal) will prevent this rise of pulse rate.

β-Blocking agents also protect the myocardium from the arrhythmias produced by hydrocarbon anesthetics and cardiac glycosides[11] and are particularly effective against ventricular arrhythmias.

β-Blocking agents must be used with caution for they may precipitate heart failure.[1] They must never be given to patients with a pheochromocytoma without simultaneous α-receptor blockade for when given alone they cause a rise of blood pressure in these patients, since the vasoconstrictor α receptor activity of epinephrine is unopposed by the vasodilator β-receptor effect.

On the basis of the above considerations a program of combined α and β-receptor blockade has been advanced for the preoperative and operative management of excision of a pheochromocytoma.[11] It is recommended that 3 days before the operation phenoxybenzamine should be administered intravenously in an amount which will reduce the blood pressure to a basal level of about 110/70 mm. Hg. The required dose is about 1 mg. per kilogram of body weight. The following day this dose should be repeated and a test dose of propranolol (40 mg.) should be administered by mouth to slow the pulse rate to 80 beats per minute; if 40 mg. fails to do so after 2 hours, a further 40 mg. is given. On the day before the operation these doses of phenoxybenzamine are repeated. On the morning of operation no phenoxybenzamine is given unless the blood pressure exceeds 160/100 mg. Hg. The pulse rate is reduced to 80 beats per minute by orally administered propranolol. The recommended premedication is papaveretum and hyoscine and the recommended anesthetic agent is thiopentone which is administered slowly and in the minimum dose that is necessary to induce anesthesia. A too rapid administration of excessive amounts of this anesthetic agent results in myocardial depression and prolonged hypotension.

Combined α and β-adrenergic blockade relieves the anesthetist from anxiety about hypertensive and hypotensive crises and death from ventricular arrhythmias in the patient, but complicates the anesthetist's task as it removes some of the cardinal signs of blood loss and overtransfusion. Since the circulation is fully expanded and compensatory vasoconstrictor reflexes have been blocked, hemorrhage is followed by a rapid fall of blood pressure without an increase of pulse rate. Excessive replacement of blood may not be accompanied by a rise of arterial pressure if the heart is failing. In these circumstances it is imperative to monitor both arterial and venous pressures continuously throughout operation. A fall of both arterial and venous

pressures indicates a fall of circulating volume which must be corrected by the administration of blood the adequacy of replacement is assessed by the return of the venous pressure to normal. These tumors are very vascular and hemorrhage is a very real hazard of their excision

Absolute complete α and β-adrenergic blockade is not desirable in practice since it is an advantage if some rise and fall of blood pressure can occur when the tumor is handled and a slight fall can occur when the tumor is removed Some latitude is required in this respect for the tumor may not have been localized before the operation and bilateral or multiple tumors may be present. The surgeon can then search the abdomen and squeeze any doubtful structure a rise of pressure indicates that a tumor may be located at this site When the tumor is removed failure of the blood pressure to fall will arouse suspicion that another tumor is present

Although preoperative and operative management along the lines mentioned above has reduced the operative risk the removal of a pheochromocytoma is still a potentially hazardous procedure and a successful outcome depends largely upon the coordinated efforts of a trained team of physician pharmacologist anesthetist and surgeon.

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cle (LV 1) (3) the anterior papillary muscle of the left ventricle (APMLV) (4) the posterior papillary muscle of the left ventricle (PPMLV) and (5) the left ventricular wall at the base of the posterior papillary muscle (LV 2) Of the 2 sections prepared from each site one was stained with hematoxylin and eosin and the other with Lawson's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. Sections were reviewed independently by two observers, and the degree of fibrosis present was graded according to the following criteria (Fig 1) grade 0 normal muscle grade 1 occasional small areas of interstitial fibrosis grade 2 multiple focal scars and small areas of interstitial fibrosis grade 3 single conglomerate scars as well as interstitial fibrosis grade 4 large and multiple conglomerate areas of scarred myocardium Islands of intact muscle remaining grade 5 extensive scar usually with gross atrophy of papillary muscle

In order to compare the degree of fibrosis in the various sites and conditions, an *index of fibrosis* was determined in the following manner For each condition and site the grade of fibrosis for each case was added and the sum divided by the total number of cases of that particular condition. Thus yielded an index of fibrosis for that site among all the cases with the condition concerned

Of the 84 patients included in the study left ventricular angiograms had been done in 19 These were reviewed for the presence or absence of mitral insufficiency Using the grades of fibrosis of papillary muscles which had been determined for these cases, an index of fibrosis of the papillary muscles was calculated for those cases with mitral insufficiency and for those with competent mitral valves.

Results

Prevalence of fibrosis Among the control hearts no fibrosis of papillary muscles was observed in infants or children but some degree of fibrosis was commonly present in the hearts from adults. Thus yielded a value of about 30 per cent for some degree of fibrosis of papillary muscles among all the control hearts (Fig 2) In each disease state however the percentage of cases with fibrosis of the papillary muscles of some degree was greater than in the controls. The greatest prevalence of fibrosis

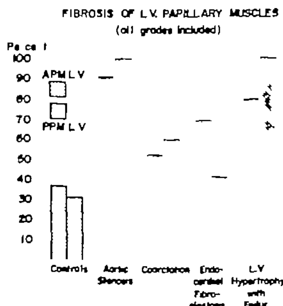


Fig 2. Prevalence of fibrosis in left ventricular papillary muscles regardless of grade according to underlying condition.

occurred among patients with aortic valvular stenosis. The prevalence of fibrosis in coarctation of the aorta and in endocardial fibroelastosis was less than in the two foregoing conditions but greater than in the control hearts.

To determine changes in the degree of fibrosis which might occur with age the cases were divided into two categories: children and adults. Comparisons were also made of the index of fibrosis in each of the ventricular sites in each of the cardiac conditions. The results of these analyses are shown in Figs. 3 and 4.

Index of fibrosis in infants and children (*Fig. 3*). Among the control cases of infants and children, fibrosis was not observed. In aortic stenosis the index of fibrosis of the left ventricular papillary muscles was 4, indicating a severe degree of change, while lesser degrees of fibrosis *were in the left ventricular wall near the* papillary muscles. Fibrosis of papillary muscles was also present in the patients with coarctation of the aorta and primary endocardial fibroelastosis but was of less severity than in aortic stenosis, with marked variation in the grades of fibrosis among the cases with a particular lesion. In several cases of coarctation of the aorta with coexistent ventricular or atrial septal defects, the papillary muscles were normal. In the few cases with associated right ventricular hypertrophy, mild fibrosis was present in the papillary muscle of the right ventricle.

Index of fibrosis in adults (*Fig. 4*). Among the control hearts from adults, the index of fibrosis was highest in the papillary muscles of the left ventricle, the highest grade of fibrosis observed being 3. In adults aortic valvular stenosis was associated with the highest index of fibrosis of the papillary muscles. The range of fibrosis in aortic stenosis varied widely *among the cases*, with several revealing fibrosis of Grade 4 and 5 in the papillary muscles.

Among adults with coarctation of the aorta, the highest index of fibrosis was in the anterior papillary muscle of the left ventricle, with a lesser degree at the bases *of the papillary* muscles and the posterior

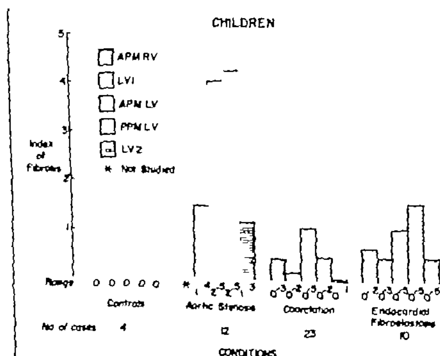


Fig. 3. In infants and children the index of fibrosis at the various sites studied, according to underlying conditions. (Right ventricular papillary muscle not studied in aortic stenosis.)

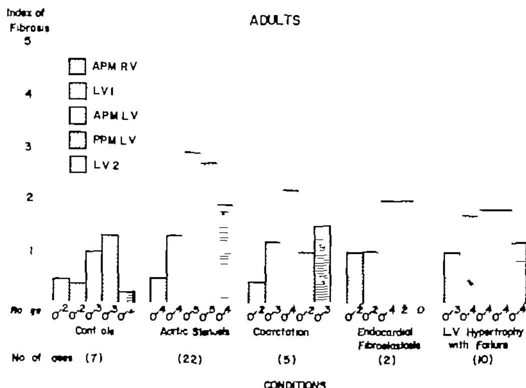


Fig. 4. In adults the index of fibrosis at the various sites studied according to underlying conditions.

papillary muscle of the left ventricle In endocardial fibroelastosis and left ventricular hypertrophy with failure the distribution of fibrosis was similar

Relation of mitral insufficiency to fibrosis of papillary muscles (*Table I*) Of the 84 patients in this study from whom specimens had been obtained left ventricular angiography had been performed in 19 as part of the diagnostic study during life In 15 of these patients mitral regurgitation had been demonstrated Eight of the 19 patients with left ventricular angiograms were infants, and in each mitral regurgitation had been demonstrated Primary endocardial fibroelastosis was present in 3 and aortic valvular stenosis in the remaining 5 cases. Of the 11 adult patients so studied mitral regurgitation had been demonstrated in 7 In the latter aortic stenosis was present in 6 and coarctation of the aorta was present in the seventh The average index of fibrosis of the left ventricular papillary muscles in the 15 subjects with demonstrated mitral insufficiency was 3.3 while in the 4 patients with angiocardiographic demonstration of competent mitral valves the average index of fibrosis was 1.5

Comment

In previous studies on anomalous origin of the left coronary artery from the pulmonary trunk and on aortic valvular stenosis in infants,[3] it appeared that each condition was commonly associated with clinical and angiographic evidence of mitral insufficiency The valvular incompetence was believed to result from infarction with secondary fibrosis of the left ventricular papillary muscles. In patients with anomalous origin of the left coronary artery from the pulmonary trunk the infarction is related in part at least to the coronary arterial abnormality while among the infants with aortic valvular stenosis the mechanism was not clear In another study[4] mitral insufficiency was commonly found in infants with primary endocardial fibroelastosis. Structural abnormalities of the papillary muscles were thought to be responsible for the valvular abnormality

Table I Indices of fibrosis of left ventricular papillary muscles according to angiographic evaluation of the functional status of the mitral valve (ranges appear in parentheses)

Mitral insufficiency (7 adults 8 children)			Competent mitral valve (4 adults)		
Anterior	Posterior	Both	Anterior	Posterior	Both
3 4 (1 5)	3 2 (1 5)	3 3 (1 5)	2 2 (1–4)	75 (0–2)	1 5 (1–4)

but histologic study of the papillary muscles had not been performed The present study indicates that fibrosis of the left ventricular papillary muscles is commonly found in this condition This histologic change may have an important influence in the generation of mitral insufficiency in endocardial fibroelastosis.

Infarction and fibrosis of papillary muscles is commonly observed among cases of infarction of the left ventricular wall in the region of basal attachments of the papillary muscles. Mitral insufficiency has been associated with this change It is probable that the mitral insufficiency observed in our cases is likewise associated with dysfunction of the papillary muscles resulting from fibrosis.

The fibrosis of papillary muscles noted in our cases is interpreted as resulting from myocardial infarction Indeed in some of the infants necrotic muscle was found in association with scar tissue The basis for a tendency to focal infarction of the myocardium and in particular of the papillary muscles in the several states studied needs discussion. It is likely that the hypertrophied myocardium increases the resistance to perfusion of the myocardial capillaries. The arteries of the papillary muscles have a greater distance to traverse[4] than do the arteries of the free wall of the left ventricle. All other conditions being equal this would appear to make the papillary muscles particularly vulnerable to infarction

Summary

The papillary muscles of the left ventricle the related left ventricular wall and the anterior papillary muscle of the right ventricle were studied for histologic evidence of and extensiveness of fibrosis. In addition to controls, in several conditions associated with left ventricular hypertrophy necropsy specimens of heart without significant coronary disease from 84 cases including 45 from infants or children and 39 from adults with a variety of disease states were studied The conditions included aortic stenosis, coarctation of the aorta endocardial fibroelastosis, and left ventricular hypertrophy with failure. In none was coronary atherosclerosis present

In each condition studied the degree of fibrosis observed in the left ventricular papillary muscles was greater than that observed in control hearts. There was direct relationship between severity of fibrosis and the angiographic demonstration of mitral insufficiency

The common denominator was left ventricular hypertrophy which appears responsible for the scarring of the left ventricular papillary muscles. Mitral valvular insufficiency may result in those cases with extensive scarring of the left ventricular papillary muscles.

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Hemodynamic effects of rapidly injected hypertonic solutions into the heart and great vessels

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Although angiocardiographic contrast media were originally intended for diagnostic purposes, a number of investigators have utilized angiocardiographic methods in investigations of cardiovascular hemodynamics.[1-4] An unstated assumption of this latter type of study is that rapid injection of contrast media has a negligible effect on the hemodynamic status of the subject. Intra-arterial injections of contrast media have been shown to produce vasodilatation and increased blood flow in dogs, cats, and human beings.[5-8] Using vena caval injections, Read and Meyer demonstrated a profound lowering of peripheral resistance, pulmonary hypertension, and even death of the experimental animals.

Newer contrast agents, usually with reduced osmolarity and viscosity, have been shown to be less toxic to the kidneys,[u] central nervous system,[u,12] and intestines. We wondered if these newer agents might not exhibit a parallel decrease in hemodynamic effect. The present study was designed to study the magnitude of these hemodynamic effects.

The hemodynamic effect of rapid injections of hypertonic solutions must be separated into those due to rapid injection of any solution and those due to hypertonicity. The effects of rapid injections of isotonic solutions were described in a previous paper.[u] The purpose of this study was to estimate the hemodynamic effects of hypertonic solutions, particularly angiocardiographic contrast media, under conditions closely simulating clinical investigative use.

Methods and materials

The methods that were employed were essentially those of the previously reported study of injections of isotonic solutions.[u] The effects of injections of contrast media into the aorta were studied in 11 dogs, while injections into the right atrium or ventricle (RA or RV) were studied in 7 dogs. Injections of hypertonic saline or dextrose solutions were studied in an additional 9 dogs. The same catheter, a 50 cm. No. 7 NIH catheter, was used for all injections to ensure comparability of the delivery system.

After the catheters were placed, systemic artery pressures, pulmonary artery pressures, and respirations were recorded to establish baseline values. Injections of

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hypertonic solutions and contrast material (Table I) were made by a hydraulic injector* at a pressure of 750 p.s.i. unless otherwise stated. Because of the varying viscosity of these materials the actual flow rates varied.[1] Successive injections of prewarmed (37° C.) solutions were made at intervals of not less than 6 minutes. Movies (16 mm.) were taken of each (1 c.c. per kilogram) injection of contrast medium to screen injection sites and the degree of coronary artery filling. At intervals that ranged from 2 to approximately 6 minutes after injection cardiac outputs were determined from indicator dilution curves which employ single rapid I.A. injections of indocyanine green with femoral artery sampling. Preliminary experiments had shown that the contrast media interfered with the recording of dye curves immediately after injection.

Maximum reactions were measured at the point of maximum pressure difference from that preceding the injection. Systolic and diastolic recovery times were measured to the point where pressure returned to within 2 mm. Hg of the preinjection pressure. All pressures were measured during expiration for easier comparison since expiration normally was of longer duration than inspiration.

Results

Aortic injections of contrast media. A typical reaction is illustrated in Fig. 1.

*C. ed. Intermatic Angiocardiograph, Cordis Company, Miami, Fla.

The changes which are illustrated are similar to those encountered with normal saline except that the duration of the response was longer. The duration of the systemic artery reaction was prolonged to an average of 5 times that of the normal saline injections. Systemic arterial pressures were reduced to an average of 27 per cent below the control value. This is essentially the same as following rapid injections of isotonic solutions (38 per cent) ($p < 0.20$).

A number of minor variations of these pressure changes occurred with contrast media. For example, periods of transient systemic hypertension were seen to be followed by hypotension and then succeeded by hypertension in 7 instances. Slow oscillations were also common (Fig. 1) perhaps due to the fact that baroceptors were striving for a new equilibrium position. In 4 instances aortic injections were followed by only systemic arterial hypertension. No clear-cut relationship of type or severity of reaction was associated with any particular contrast media.

An increase in the amount of the injectate caused a corresponding decrease of systemic arterial pressures and an increased length of the recovery period (Fig. 1). Systolic pressures were lowered an average of 11, 15, and 21 per cent for ½, 1, and 2 c.c. per kilogram injectates, respectively.

In contrast to the isotonic saline injections,[13] injection of contrast media frequently caused changes in heart rate. Both transient tachycardia and bradycardia

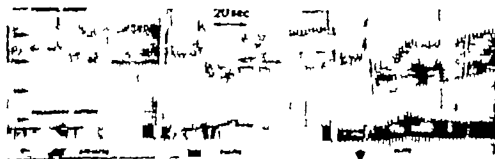


Fig. 1. Doses of ... -Contra ... in ... ing qua ... ties int ... the aortic r ... at the same inject ... n pressure 750 p. ... L Not ... the positiv ... correlation of increased dosages with both d ... ration and degree of bl ... d pressure ch ... nges. The pressure scales in this and all subsequent figures are ... millimeter of mercury.

were noted. There was no correlation of changes of the pulse rate either with a particular contrast media or with the degree of coronary artery filling.

Respiratory rate was also commonly affected. Apnea or gasping respirations frequently accompanied aortic injections of contrast media particularly with the larger injection volumes.

Generalized tonic-clonic convulsive seizures occurred in only one dog after a total of 35 c.c. per kilogram of 90 per cent Hypaque was injected. This amount had been given in 3 separate injections over a period of 14 minutes.

Injections of contrast media into the right atrium. In general injections into the right atrium produced smaller pressure changes than intra-aortic injections. Fig. 2 illustrates a typical experiment. Significant transient pulmonary hypertension was found in 5 of the 7 dogs which were studied. The average increase was 70 per cent over the control value with a range of 6 to 78 per cent.

Systemic artery blood pressures in

Table I. Contrast media employed listed in order of increasing osmolarity

Chemical name	Commercial name	Iodine content (per cent)	Viscosity at 38° C. (cp)	Osmolarity (mOsm./L.)
Methylglucamine diatrizoate	Renografin (60 per cent)	29	4 06	1 360
Sodium diatrizoat	Hypaque sodium (50 per cent)	30	2 30	1 376
Methylglucamine iothalamate	Conray (60 per cent)	28	4 38	1 382
Methylglucamine diatrizoate	Renografin (76 per cent)	37	8 89	1 648
Sodium and methylglucamine diatrizoate	Renovist (37 per cent)	37	5 71	1 815
Sodium and methylglucamine diatrizoate	Hypaque M (90 per cent)	46	19 20	2 020
Sodium iothalamate	Angio-Conray (80 per cent)	48	7 98	2 264



Fig. 2. Injection of 1 c.c. per kilogram of Renovist into the right atrium at 750 p.s.i. The respiratory rate increased from 14 to 22 per minute. The open arrow denotes the return of femoral artery systolic pressure to preinjection values after about 70 seconds. Systemic arterial diastolic pressure and pulmonary artery systolic pressure did not return to preinjection values within the time period shown in this figure. Note particularly that the changes in pressure follow immediately after injection of contrast material. The blank areas in the pressure tracings are due to interruption of the light beams for trace identification.

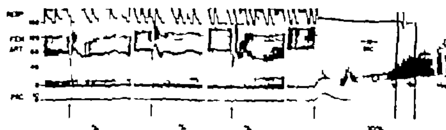


Fig 3 The effect of injection of increasing concentrations of solutions of sodium chloride, 1 c.c. per kilogram t 750 p.s.i. i t the right entricle of Dog 27 (weight, 10 kilograms). Premature ventricular contractions oc urred after each injection w th resultant systemic arterial hypotension This was followed by brief period of hypertension for ll except the most concentrated solution (10 per cent). For the lowest 3 concentrations, sy temic arterial h potension of approximately the same degree and duration then occurred. Ten per cent N Cl produced profound temic arterial hypotension, p lmonary artery (PA) and pulmonary capillary (PAC) hypertension and pnea followed by tachypnea



Fig 4 I jection of 0 5 per kilogram of ex tremel concentrated sodium chloride sol tion (10 ml 9 000 mOsm per liter) into the right atrium of 20 kilogram dog produced ha ges that were similar t the injections of t ice the amou t of 10 per cent N Cl (pproximat ly 3,000 mOsm per liter)

creased immediately and this was followed in every instance by a period of hypotension. Recovery often in an oscillatory manner to preinjection pressure levels occurred more rapidly than after the aortic root injections (compare Figs. 5 and 6)

Arrhythmias occurred in all except two instances. Most of the animals exhibited a short period of bradycardia which was followed by moderate tachycardia.

Cardiac outputs increased an average of only 5 per cent over control values (−? to +17 per cent) when they were measured 2 minutes after the injection In 1 instance cardiac output remained significantly elevated for more than 6 minutes but in the remaining dogs, cardiac output had returned to control levels by that time

Increases in respiratory rates occurred but they were not as striking as those following intra-aortic injections. No convulsions occurred in this group

Injection of hypertonic solutions Hypertonic solutions of sodium chloride and dextrose were injected in the same manner into the right heart (RA and RV) of 6 dogs and into the aorta of 3 additional dogs. Representative effects of right heart injection are shown in Figs. 3 and 4 In general there was an increasing degree of femoral artery hypotension and pulmonary artery and pulmonary capillary hypertension with increasing concentration of injected material (Figs. 5 and 6) Injection of so small an amount as 0.5 ml. per kilogram of a highly concentrated NaCl solution (9000 mOsm./L) caused profound cardiac rhythm disturbances, systemic arterial hypotension and pulmonary artery hypertension (Fig 4) Tachypnea followed the lower concentrations, whereas apnea and then tachypnea resulted from injection of the more concentrated NaCl solutions. Concentrated dextrose solutions were similar in effect to the NaCl

For right heart injections, the effects on the cardiorespiratory system were proportional to the osmolarity (Fig 5) The degree of femoral artery hypotension and pulmonary artery hypertension cor

related well with the osmolarity but pulmonary artery wedge pressure showed a significant rise only with 10 per cent NaCl. Aortic injections produced a strikingly different picture (Fig. 6). Changes in femoral artery and pulmonary artery pressures were similar to those produced by normal saline. Pulmonary artery wedge pressures, on the other hand, correlated remarkably well with osmolarity (r = 0.89). We are unable to explain these differences.

As it was mentioned earlier, technical difficulties, interest in monitoring pressures in a relatively undisturbed state, and also interference with recording indicator dilution curves in the presence of contrast media precluded measuring cardiac outputs prior to approximately a minute and a half after injection. Unfortunately, measurements after this period of time were generally within accepted range of error of the indicator dilution method, that is less than 10 per cent. Data obtained from electromagnetic flowmeters[8] indicate that the injection of isotonic solutions into the right ventricle caused an increase in a left ventricular stroke volume which returned to preinjection values in about 15 seconds. Injections into the left ventricle were followed by an initial increase in stroke volume for about 15 seconds and were then followed by about 45 seconds of decreased stroke volumes. Thus, many of the important changes in cardiac output had already occurred before our initial dye curve.

Changes in cardiac output after left heart injections of various hypertonic solutions and also 0.9 per cent saline were within the errors of the method when they were measured after 2 minutes. Injection of various concentrations of dextrose solutions into the right heart also produced no significant changes in cardiac output. Only increasing concentrations of sodium chloride when it was injected into the right heart, appeared to produce any pattern of cardiac output changes. Injections of normal saline and of 3 per cent and 5 per cent NaCl all produced increases in cardiac output which ranged from 13 to 71 per cent. Injections of 7½, 10, or 14 per cent NaCl, on the other hand, resulted in no change in 7 instances and lowered cardiac outputs in 2 instances (32 and 63 per cent). Thus, injections of isotonic, 3 per cent, and 5 per cent NaCl acted in a manner similar to that reported by Hallerman and associates[18] by, namely, increasing the volume presented to the left ventricle and increasing left ventricular stroke volume. Concentrations of NaCl of 7½ per cent and greater were followed by a more prolonged period of decreased cardiac output on 2 occasions.

While the hemodynamic effects of contrast media have been blamed primarily on their hypertonicity[1,9] (Table I), they differ from other hypertonic solutions in the greater duration of their effects. Figs. 5 and 6 show clearly that contrast media upset the circulation for a significantly longer period of time than solutions of NaCl or dextrose of comparable osmotic activity. For example, systemic arterial hypotension persisted for an average of 3.0 minutes (range 0 to 7.1 minutes) after an injection of contrast medium (with a concentration range of 1,360 to 2,260 mOsm per liter into the aorta. Sodium chloride solutions in a range of 310 to 2,660 mOsm per liter never produced hypotension that lasted more than 1 minute. Perhaps the larger organic molecules of contrast media persist longer within the circulation or have direct effects on the cardiovascular system.

Discussion

In general, the newer contrast media employed in this study were better tolerated by experimental animals than those employed by Read.[9] None of our dogs died, whereas ten of Read's did. The only agent employed in both studies was 90 per cent Hypaque. Injections of 3 ml. per kilogram resulted in death in 4 out of 6 dogs in Read's study. It is likely that the cumulative doses of contrast were also greater than in our study.

However, all of these newer agents also caused marked hemodynamic changes. These changes were shown to be related to dosage rates and injection pressure. Injections of isotonic saline, dextrose solutions, and whole blood also caused significant systemic and pulmonary pressure changes, regardless of whether injection was into the right or left heart.[16] The

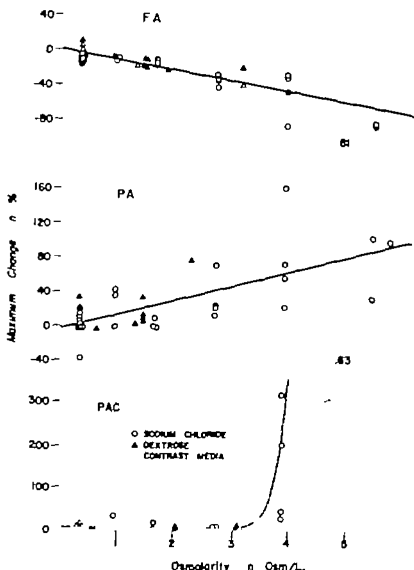


Fig. 5. The effect of rapid injection of solutions of varying osmolarity in the right side of the heart on maximum pressure changes. A linear least-squares technique was used to fit the data of the NaCl and dextrose solutions for all except maximum pulmonary artery wedge pressures, the technique for which was obviously not linear. In general, both maximum pressure changes and recovery times were proportional to osmolarity. The maximum pressure changes recorded for contrast media were similar to those of NaCl and dextrose solutions. However, the recovery times were significantly longer for angiographic contrast media.

effects of hypertonic solutions and contrast media were similar but more prolonged. Fig. 7 demonstrates clearly that iodine per se is not the cause of the hemodynamic changes.

It would appear likely that at least mechanisms are at play after rapid injection into the cardiovascular system. Initially, there is a local increase in pressure due to rapid injection of fluid. This is followed by systemic hypotension possibly of carotid sinus origin. The genesis of the pulmonary artery pressure changes is less clear. Although Eliakim and associates[20] postulated this was due to spasm at the pulmonary vein–left atrial junction, the demonstration of increased left atrial and left ventricular end-diastolic pressures by Friesinger and colleagues[7] is contrary to this theory. Read and Meyer postulated that red cell agglutination in the pulmonary bed accounted for this phase

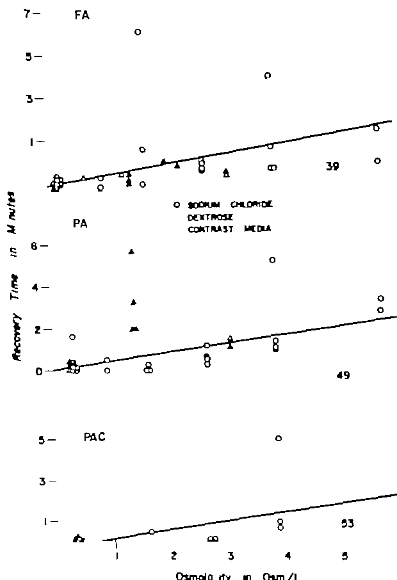


Fig 5B The effect of rapid injection of solutions of varying osmolarity in the right side of the heart on recovery times. See legend Fig 5 1

of the reaction, but injections into the right atrium which should result in a higher concentration of contrast media in the pulmonary vascular bed were less striking than intra-aortic injections in the present study. Similarly red cell agglutination would not account for the increases in systemic arterial flow noted by Sako the increased left atrial pressures that were observed by Frieninger and associates,[21] nor the increased pulmonary artery wedge pressures which were seen in the present study after aortic injections.

An alternate possibility lies in an increase of pulmonary venous pressure which is due to the stimulation of pulmonary venous chemoreceptors.[22,23] The production of bradycardia, systemic hypotension, and apnea after injection of hypertonic solutions suggests the activation of chemoreceptors is due to the Bezold Jarisch effect.[24]

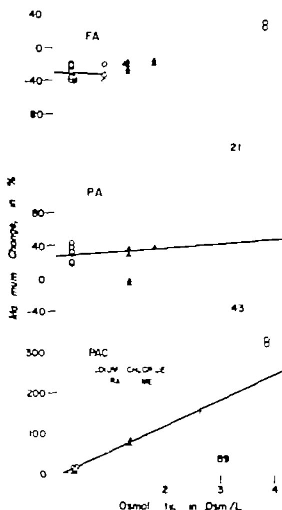


Fig 6A The effect of rapid injection of solutions of varying osmolarity into the left side of the heart on maximum pressure changes. The pressure changes that were recorded after contrast media were similar to those of sodium chloride solutions.

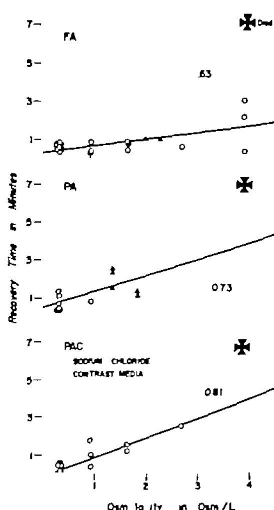


Fig 6B The effect of rapid injection of solution of varying osmolarity into the left side of the heart on recovery times. See legend Fig 6A Compared to NaCl solutions of equal osmolarity there was significant increase in the time that was needed to return to preinjection pressures after injection of contrast media.

Rapid injections of isotonic solutions produce hemolysis with release of ATP a potent vasodilator[22] The authors believe that this is a major hemodynamic effect of rapid injections of isotonic solutions.

As can be seen from Table II rapid injection produces several thousand times the minimum power needed to fragment red blood cells (approximately 10 to 20 $\times$ 10³ dyne-cm per second)[23] Andres further showed that only 0 09 ml of blood hemolyzed per minute produced a sevenfold increase in total blood flow over the preinjection resting value Since the usual period of injection is less than 2.5 seconds the amount of total hemolysis is extremely minute and failure to detect this is not surprising[22]

The hemodynamic effects that occur after the first few seconds are best explained by the high osmolarity of the substances which are injected (Table I) Even relatively slow injections of hyper tonic solutions have been shown to produce these changes.[24] Smaller and more rapid changes were observed after rapid injection of isotonic NaCl and NaI (Figs. 3 and 7) Profound systemic hypotension pulmonary hypertension bradycardia, and apnea were produced by rapid injection of 10 per cent NaCl When solutions of less than 1,500 mOsm per liter are injected the predominant response is sys-

temic hypotension consistent with peripheral vasodilatation[8] or to hemodilution and resultant viscosity changes.[28]

It appears to us that all of the above mechanisms may be called into play after injections of contrast media into the circulation. The relative importance of these effects will be determined by a complex and as yet, undefined inter-relationship between the site of injection, the rapidity of injection, and the osmotic concentration of the particular contrast medium. The wide array of minor variations of the hemodynamic changes observed by us might best be accounted for by such a multivariable schema.

All of these agents caused sufficient hemodynamic changes that their employment to investigate hemodynamics is of doubtful validity. Bruce and associates[1] injected 2 ml. of 90 per cent Hypaque per kilogram of weight into the pulmonary arteries of dogs in an experimental evaluation of cardiac control mechanisms. From our data, this in itself would appear to have been a significant enough hemodynamic stimulus to obscure the meaning of the experimental changes, since these were of approximately the same order of magnitude. A similar criticism may be leveled against the use of contrast media to investigate drug effects on the coronary arteries[2] since hypertonic solutions are in themselves potent vasodilators. Perhaps the most questionable example in this regard is the use of contrast media to investigate the functional patency of the ductus arteriosus. Since these contrast agents usually cause an increase in pulmonary artery pressures and a simultaneous decrease in aortic pressures, it is quite possible that this might cause an erroneous interpretation of closure when the ductus in reality was open. A left-to-right shunt through the ductus of normally small magnitude might cease altogether after injection of contrast media.

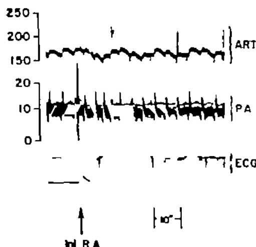


Fig. 7. Injection of 10 ml. of isotonic sodium iodide solution (300 mOsm. per liter) into 20 kilogram dog produced effects that were similar to those of isotonic sodium chloride. Thus, the hemodynamic effects of contrast media are related to their high osmolarity and not to the presence of iodine.

Summary and conclusions

The effects of rapid injections of varying concentrations of saline, dextrose, and angiocardiographic contrast media on systemic and pulmonary pressure and cardiac output were investigated in mongrel dogs.

Table II. Kinetic energy of 3 representative fluids

Fluid	Injection through a 7F 50 cm. NIH catheter at 750 p.s.i.					
	Density at 37° C. (Gm./ml.)	Viscosity at 37° C. (cp.)	Average velocity (cm./sec.)	Reynolds' number	Delivery rate (Gm./sec.)	Kinetic energy (dyne cm./sec.)
Distilled water	0.993	0.68	1140	42.3×10^3	57.3	3.7×10
Hypaque (50 per cent)	1.303	2.30	890	12.8×10^3	58.8	2.3×10^7
Hypaque-M (90 per cent)	1.505	19.20	490	0.93×10^3	37.6	4.5×10^6

*Experimental value.

Although there were wide variations in magnitude injections of contrast media into either the right atrium or aorta, usually caused systemic hypotension pul monary arterial and pulmonary capillary hypertension Investigations of hemody namics with the use of contrast agents should be checked for arrhythmias and pressure changes that occur during the period of visualization and the results should be weighted accordingly

The authors wish knowledge the valuable technical assistance of Sch yler Hardm Pat Mock Phoebe Collins F E hridge Paul Byerly and J An Ryals W ish t thank E R Sq ibb and Sons for supply g he Renovist and Renografin nd M ll nckrodt Pharmaceuticals for supplying A gioConr and C n

W also sh t thank D Gerold L. Schiebler of the Departmen of Pediatrics and Dr Wendell N St ainb of the Department of Physiology for their ma helpf l omment nd criticisms during the urse of this tudy

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Cardiopulmonary function in Fallot's tetralogy after palliative shunting operations

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It has been 20 years since Blalock and associates[1] and later Potts and associates[2] introduced shunting operations for the palliative treatment of patients with Fallot's tetralogy. Reports have described the clinical follow-up of these patients[3-5] and the development of pulmonary hypertension after the operation in man or animals,[6-8] but there has been little discussion of other aspects of cardiopulmonary function. This report presents the cardiac catheterization data from 21 patients with Fallot's tetralogy in whom a surgically produced aortopulmonary shunt had been present for at least 5 years, and the results of pulmonary function or exercise studies on 14 of these patients.

Material and methods

The clinical data are summarized in Table I in which the cases are arranged in ascending order of mean pulmonary artery pressure. At the time of this study the age range was 8 to 37 years, with a mean of 15 years. All but 2 of the patients were less than 20 years old. All patients had been cyanotic before surgery. A surgical shunt had been present for an average of 10 years (range 5 to 15 years). They were studied to assess whether the defect should be repaired completely.

The right sides of the hearts of the patients who were admitted to the hospital for study were catheterized with standard techniques. Pulmonary arterial pressure was measured in all 21 patients, pulmonary wedge pressure in 17, pulmonary vascular resistance in 15, and oxygen consumption and pulmonary and systemic blood flows in 18. Blood samples were analyzed for oxygen content by the spectrophotometric method of Nahas,[14] or of Van Slyke and associates.[15] Pulmonary venous saturation was assumed to be 97 per cent when the patient breathed air. Expired air was collected in a Tissot spirometer and analyzed for oxygen and carbon dioxide with the micro-Scholander technique.[12] Blood gas tensions and pH were determined with oxygen and carbon dioxide electrodes[13] and a Beckman pH meter.

Ten patients exercised in a sitting position on a cycle ergometer. One patient also exercised in the supine position during

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Table I. Clinical data in 21 patients with Fallot's tetralogy

Patient No.	Age	Sex	Height		Weight		Shunt type	Duration (yr.)	Disability grade*	M.P.A.† (mm. Hg)	Pulmonary pathology microscopic findings
			Cm.	Percentile	Kg.	Percentile					
1	8	F	116	3	19.8	5	B‡	5	II	8	
2	17	F	159		44.5		B	10	III	10	Normal
3	11	F	139	25	27.7	5	B	10	III	11	Normal
4	12	F	150	40	35.6	25	B	8	III	12	
5	13	M	160	60	43	50	B	9	II	13	
6	10	M	135	25	29	20	B	9	II	13	
7	15	F	160	40	54	60	B	9	III	13	Normal
8	15	M	161	50	53	75	P	12	II	13	
9	18	M	180		70		B	13	II	15	Normal
10	37	F	165		54		B	8	III	15	
11	12	F	154	30	32	10	P	9	III	18	
12	21	F	163		49		B	11	IV	18	Multiple small arterial thromboses
13	9	M	129	10	25	8	P	8	II	20	
14	12	M	140	3	26	3	P	9	II	22	
15	12	M			34.3	25	B‡	8	II	25	
16	16	M					P	9	II	26	
17	11	M	138	10	27	3	P	10	II	38	Slight scattered arterial intimal thickening
18	13	M	148	20	43	50	P	9	II	39	Slight intimal thickening focal atheromatous plaques
19	16	M	159		41		P	13	II	42	
20	17	F	173		56		B	15	III	50	
21	12	F	137	3	25	3	B	10	III	57	Slight atherosclerosis of large pulmonary arteries

*Disability graded according to standards recommended by the New York Heart Association.
†Abbreviations: B, Blalock type anastomosis; P, Potts type anastomosis; M.P.A., mean pulmonary artery pressure.
‡Blalock anastomosis 4 years of age clinically unsuccessful.

cardiac catheterization. Heart rate was measured from an electrocardiograph and changes in arterial oxygen saturation were recorded continuously with a Waters-Conley ear oximeter. Ventilation and oxygen consumption were determined during the last 2 minutes of a 6-minute period of exercise at each load. Exercise was continuous and the load was increased every 6 minutes until either the patient or the physician felt that the exercise should be stopped.[1] Arterial blood samples were obtained from 3 subjects during exercise; oxygen and carbon dioxide tensions, pH, and oxygen saturation were measured. In these patients, the oxygen saturation of arterial blood that was recorded by the ear oximeter was compared with that obtained by analysis of arterial blood samples by the Van Slyke method; the difference averaged 3 per cent.

Measurements of lung volumes, forced expiratory volume in 1 second, and distribution of inspired gas were made in 13 patients by standard methods,[1] and compared to published normal values.[7,11] The diffusing capacity for carbon monoxide was determined in 9 patients by the

Table II *Results of cardiac catheterization in 21 patients with Fallot's tetralogy*

Patient A	P A P (syst./diast.) (mm Hg)	Qp (L./min)	Q (L./min)	Ppc( ) (mm. Hg)	P V R (mm Hg/L./min)	T P R (mm. Hg/L./min)	Interval O saturation (per cent)	
							Patient supine	Patient pright
1	13/5	3 4	3 8	6	0 6	2 4	82	77
2	15/7	4 8	5 0	6	0 8	2 1	88	70
3	20/6	3 6	3 7	9	0 6	3 0	88	
4	20/10	4 0	4 2	7	1 2	3 0	82	80
5	18/7	3 6	4 2	10	0 8	3 6	89	76
6	13 (mean)						86	
7†	13 (mean)		3 5	7			87	85
8	22/8	6 0	4 2			2 2	92	
9	21/8	8 0	6 2	6	1 1	1 9	92	80
10	21/10	4 7	3 5	6	1 9	3 2	92	85
11	27/10	15	3 9			1 2	95	93
12‡	18 (mean)	3 6	4 1	10	2 2	5 0	70	
13	28/17	16	3 5	12	0 5	1 2	92	91
14	28/17	8 6	2 7			2 6	91	
15§	37/19		4 7	14			89	
16	35/21	18	3 3	15	0 6	1 4	96	93
17	53/30	>20	2 4	15	<1	2	96	
18	58/30	19	6 7	8	0 8	2 0	91	88
19	55/34	>20	5 4	24	<2	2 5	92	92
20	67/43	>20	3 6	8	<2	2 5	92	89
21	67/43	12 0	2 3	15	3 5	4 8	94	

Adequate phasic pulmonary artery pressures were not obtained in several cases. Mean pulmonary artery pressures are listed in Table I.
Abbreviations: P A P, pulmonary artery pressure; Qp, pulmonary blood flow; Qs, systemic blood flow; Ppc(v), pulmonary "wedge" pressure; P V R, pulmonary vascular resistance in millimeters of mercury per liter per minute; T P R, total pulmonary resistance.
†Pulmonary artery not entered. Wedge pulmonary venous and left atrial pressures obtained after catheter had passed through small atrial septal defect.
‡Thrombosed left pulmonary artery and anastomosis.
§End to end left subclavian–left pulmonary artery anastomosis.

single breath method of Ogilvie and colleagues.[20]

Eight of the patients died in the immediate postoperative period after open heart surgery for total repair of their cardiac lesions; specimens of lung tissue for histologic examination were obtained from these.

Results

Cardiac catheterization data are summarized in Table II. The oxygen saturation of arterial blood obtained while the patient was in the supine position during cardiac catheterization varied from 70 to 96 per cent. Th verage fall in oxygen saturation when the patient stood was 6 per cent with a r nge of 0 to 18 per cent. Pulmonary blood flow ranged from slightly less than systemic flow (3 4 L. per minute) to greater than 20 L. per minute. In general, the patients with a large pulmonary blood flow had higher arterial saturation when they were resting and higher pulmonary artery pressure. Patients with a small pulmonary blood flow usually had a large decrease in arterial saturation when they changed from a supine to an upright position (Fig 1). Four of the subjects with pulmonary artery pressures greater than 5 mm Hg also had a pulmonary artery wedge pressure of 15 mm. Hg or more. Since the higher pulmonary artery pressures and pulmonary artery wedge pressures were associated with large pulmonary flows (Fig 2), pulmonary vascular resistances were generally low. In the patients in whom the pulmonary vascula resistance

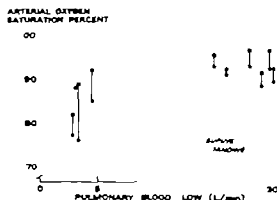


Fig 1 The total pulmonary flow at rest was plotted against change in arterial oxygen saturation on changing position from supine to standing

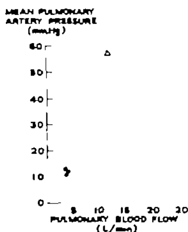


Fig 2 The pulmonary blood flow was plotted against mean pulmonary artery pressure. O patient with occluded left pulmonary artery Δ, patient with abnormal pulmonary vascular resistance

was not measured there was nothing to suggest that it might have been abnormal except in case 15 This patient had an end-to-end anastomosis of the subclavian artery to a left pulmonary artery The mean pressure in the right pulmonary artery was 25 mm Hg the pressure was not measured in the left lung If the systemic pressure had been transmitted directly to the left lung then the pulmonary vascular resistance would have been high in the left lung

The results obtained at the highest level of exercise in 10 subjects are shown in Table III Because of the differences in age and size of the patients oxygen consumption and ventilation have been expressed in milliliters per minute per kilogram of body weight. The highest oxygen consumptions during exercise were attained by those patients who had large resting pulmonary blood flows and high resting and exercise arterial oxygen saturations in the sitting position The average pulse rate at which exercise was stopped was 136 per minute (range 112 to 164) This was less than the normal maximal pulse rate of 190 per minute[11] Arterial blood gas tensions and pH in 10 patients at rest and in 3 patients during the highest exercise load are shown in Table IV Arterial carbon dioxide tension during cardiac catheterization and during exercise tended to be low in most patients and pH was usually raised which indicated hyperventilation Although oxygen tensions decreased to low levels (35 to 46 mm Hg) during exercise in all 3 patients arterial carbon dioxide tension changed in only one. Ventilation equivalents for oxygen during exercise in all 10 patients are also shown in Table IV The values usually changed little with exercise confirming that alveolar hyperventilation did not become more marked on exercise.

The results of pulmonary function tests in 13 patients are given in Table V Vital capacity was reduced below 80 per cent of predicted normal in 9 patients and residual volume was greater than 120 per cent of predicted normal in 7 of the patients. Although the number of cases was small the decrease in vital capacity appeared to be related to the pulmonary artery and wedge pressures (Fig 3) Residual volume did not show the same relationship but was highest in patients with elevated wedge pressures. The diffusing capacity for carbon monoxide was normal or increased in the 9 patients in whom it was measured The values appeared to be independent of pulmonary artery pressure and also of pulmonary blood flow The average value in 3 patients with pulmonary flows of less than 5 L. per minute was 118 per cent of predicted while that in 4 patients with flows of 15 L. per minute or more was 1[illegible] per cent

Sections of lung tissue were available from 3 patients in whom large pulmonary

Table III Results of exercise testing at maximum load

Patient No.	Maximum load (Kg M/min)	$\dot V_{O_2}$ (ml/min/Kg)		Pulse rate (per min)		$\dot Q_p$ (L/min/M²)		Arterial oxygen saturation† (per cent)		Ventilation (ml/min/Kg)	
		Rest	E	Rest	Ex	Rest	Ex.	Rest	Ex	Rest	Ex.
2	100	5	10	120	164	3.4		60	<50	190	620
4	150	6	10	72	112	3.3		80	68	190	360
5	200	7	16	98	140	2.6		76	<50	290	720
9	300	7	16	100	120	4		82	63	220	500
10	100	6	10	112	116	3.0		77	69	230	550
13	250	10	22	98	154	17		91	77	420	960
16	300	6	[illegible]	72	120	12		93		150	690
16‡	300	6	22	80	138		8	96	75		
18	150	9	22	105	150	14		91	63	200	570
19	300	8	32	94	118	20		94	87	360	820
20		5	14	115	162	16				240	620
Mean	215	6.8	18	97	136	9.5		84		250	640

Abbreviations: $\dot V_{O_2}$, oxygen consumption; $\dot Q_p$, pulmonary blood flow.
†Values obtained from ear oximeter except in patient 16 for supine exercise.
‡Supine exercise during cardiac catheterization.

Table IV Results of exercise on ventilation and arterial gas tensions and pH

Patient No.	Arterial O_2 tension (mm Hg)		Arterial CO_2 tension (mm Hg)		Arterial pH		Ventilation equivalent†	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
2	51		25		7.51		38	59
4	35	37	37	36		7.40	34	34
5	61		40		7.45		43	43
9	65		30		7.46		31	31
10	62	35	45	32	7.41	7.49	35	58
13	54		30		7.45		45	43
16	62	46	39	40	7.43	7.36	29	36
18	63		37		7.40		24	26
19	44		37		7.43		44	26
20	59		24		7.51		38	40
Mean	60	39	34	36	7.45	7.42	36	40

*Rest and exercise refer to results obtained during air breathing at rest and during the greatest sustained exercise load.
†Ventilation equivalent is expressed in milliliters of ventilation per milliliter of oxygen consumption.

flow had been present for many years and from 5 patients with smaller pulmonary flows (Table I). Of the patients whose lungs were examined histologically one patient (No. 21) had the highest pulmonary artery pressure (6/43 mm Hg) and pulmonary vascular resistance (3.5 mm Hg per liter per minute); the lungs showed evidence of only minimal vascular damage. One patient (No. 12) died after a complete surgical correction was attempted following the spontaneous thrombosis

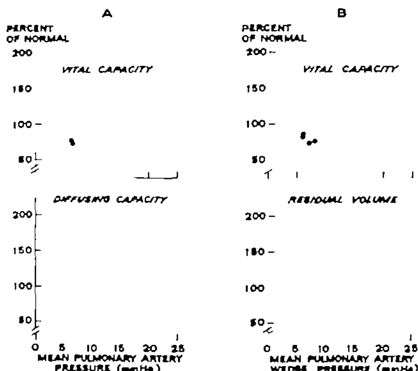


Fig. 3. The lung volumes and diffusing capacity for carbon monoxide was plotted against pulmonary vascular pressures. A, Vital capacity and diffusing capacity plotted against mean pulmonary artery pressure. B, Vital capacity and residual volume plotted against mean pulmonary wedge pressure.

bosis of the anastomosis she was found to have multiple recent thromboses throughout the pulmonary vascular bed but the pulmonary vessels were otherwise normal. There was evidence of minimal intimal thickening in 2 patients (Nos. 17 and 18) but no pathologic evidence of pulmonary vascular damage was found in the other 4 lungs that were studied at autopsy.

Discussion

Early palliative shunting operations remain procedures of choice in selected patients with Fallot's tetralogy, and reoperation for total repair is still associated with a significant mortality rate in most institutions. It is important to know whether large pulmonary flows that result from a systemic-pulmonary shunt necessarily lead to serious pulmonary vascular damage or other disability during the period of growth and how much residual disability remains in these patients, when they are evaluated by tests of cardiopulmonary function. We have attempted to answer these questions.

Most of our patients had sufficiently severe lesions to require palliative surgery in early childhood and had returned to the hospital because their systemic-pulmonary shunt seemed to be too large or too small. The highest pulmonary vascular resistance in our cases was only 3.5 mm. Hg per liter per minute in a patient of 1 M.[2] body surface area. In some patients with pulmonary blood flows near 20 liters per minute, values of less than 1 mm. Hg per liter per minute were observed. Abnormal pulmonary artery pressures (mean 25 mm. Hg or more) were found in 7 patients but large flows were also present. The wedge pressure was also high in some patients with increased pulmonary blood flow. Since these patients almost certainly had equalization of the right and left ventricular end-diastolic pressures, it is likely that relative obstruction to flow existed between the pulmonary capillary bed and the left ventricle. Rudolph and Nadas[11] have discussed this as a possible factor in the eventual development of pulmonary hypertension.

The number of cases which were studied

Table V. Results of pulmonary function testing in 13 patients

Patient No.	VC* (per cent predicted)	RV (per cent predicted)	FEV1	SBO2 (per cent N2)	TN2 (per cent N2)	Dc (per cent predicted)
1	83		80	1.5	1.0	138
2	68	83	97	1.5	0.5	86
4	100	100	85	2.0	0.5	129
5	76	190	83	1.0	0.5	
7	73	160	54	0.5	1.1	91
10	85	109	71	1.2		
11	66	220	81	1.5	1.0	135
13	88	280	100	1.9	0.3	127
15	66	150	90	1.0	1.0	113
16	45	172	87	0	1.0	
18	50	190	86	3.0	1.3	128
19	74	119	90	1.0	0.3	
20	68	90	87	3.0	0.3	100
Mean	73	155	84	1.51	0.7	116

Abbreviations and normal values: VC, vital capacity (normal, 80 to 120 per cent); RV, residual volume (normal, 80 to 120 per cent); FEV1*, percentage of vital capacity in 1 second forced exhalation (normal, > 79 per cent); SBO2, test of alveolar gas uniformity: per cent rise in nitrogen concentration during exhalation following a single breath of 100 per cent oxygen, between the volumes 750 and [illegible] ml (normal, < 1.5 per cent); TN2, per cent nitrogen remaining in end tidal gas after breathing 100 per cent oxygen for [illegible] (normal < [illegible] per cent); Dco, single breath diffusing capacity for carbon monoxide.

at autopsy was small but there seemed to be an association between intimal thickening in the pulmonary arterial tree and elevation of pulmonary artery pressure. However, the absence of physiologic or anatomic evidence of pulmonary vascular damage in other patients indicates that large pulmonary flows, resulting from an aortopulmonary shunt, may be well tolerated for many years. This is, however, not always the case and there are several examples of severe pulmonary vascular disease in the literature, but the incidence of this complication seems to be quite low.

Patients with the highest resting pulmonary blood flows (Table V) reached the highest work load and achieved the largest oxygen consumptions during exercise. The results of exercise tests did not always correspond to the clinical evaluation of exercise tolerance. The patients who had been judged on clinical criteria to have too large left-to-right shunts were generally in the relatively high exercise tolerance group. This is understandable since the major effect of an aortopulmonary shunt stems from the enlargement of the pulmonary vessels and possibly the left side of the heart, so as to increase pulmonary blood flow and increase the flow of oxygenated blood from the lungs to the left side of the heart.

The fall in arterial oxygen saturation in the standing position of patients with low pulmonary blood flow has been noted in untreated Fallot's tetralogy[22] and has been explained on the basis of a change in the distribution of blood volume with the change in position. After shunting operations, too, the decrease in saturation when the patient is standing is greatest in patients with small pulmonary blood flows. A large central pool associated with a large pulmonary blood flow tends to maintain a supply of fully saturated pulmonary venous blood to the left side of the heart. A high oxygen saturation in the standing position in these patients is an indication of a large pulmonary blood flow and a relatively good exercise capacity and is of greater significance than a measurement obtained when the patient is supine.

A striking finding during exercise was the marked fall in arterial oxygen saturation and the low level of work at which our patients had to stop. Additional in

formation about the limitation of exercise tolerance was obtained in Patient 16 (see Table III). The mixed venous oxygen saturation during exercise fell from 75 to 30 per cent, the arterial oxygen saturation fell from 96 per cent to 75 per cent, and the arteriovenous oxygen content difference increased to 108 ml. per liter. It seems likely that this value may be close to maximum, since a mixed venous saturation of 30 per cent is about that found during severe exercise in normal subjects. The level of mixed venous saturation was not measured during exercise in our other patients but presumably it was similarly reduced because their arterial oxygen saturations were low. It is possible then that the fall in arterial saturation during exercise limits exercise at a time when the cardiac output is not excessive. Another feature of the response to exercise was the low pulse rate at which our patients stopped exercise. This might be explained by hypoxia. Daly and Scott[24] have reported bradycardia during carotid body perfusion with hypoxic blood. Åstrand and Åstrand[25] described relative bradycardia in trained individuals on exercise after acclimatization at altitude as compared to sea level exercise. If one plots pulse rate against oxygen consumption and extrapolates to a normal maximum exercise pulse rate of 190 per minute, extrapolated oxygen consumptions (and work loads) fall in the normal or nearly normal range in our patients with large pulmonary flows but are well below normal in those with small shunts. Thus, it appears that patients in the former group are able to maintain a nearly normal forward stroke volume during exercise even with the burden of a large left-to-right shunt, while those in the latter are not even without a large left-to-right shunt. It is also clear that standard exercise tests based on the extrapolation of the load-pulse rate curve have no practical meaning for estimation of maximal exercise capacity in patients who become increasingly cyanotic on exercise.

We conclude that the major determinant of a relatively good exercise tolerance in our patients is a high pulmonary flow with the associated large central blood pool, high initial arterial oxygen saturation, and perhaps, a relatively normal left ventricular forward stroke volume. At best these patients were still limited when compared to normal subjects.[25] Although they attained loads which were obviously maximal or nearly maximal, most of them stopped because of pain or tiredness in the legs and only rarely was dyspnea noted.

The pattern of ventilation during exercise was interesting in that our patients failed to hyperventilate in the normal manner when their arterial oxygen saturation fell.[26] Previous papers have reported metabolic acidosis in children with severe chronic cyanosis[27] and compensated respiratory alkalosis in older less cyanotic patients, which is similar to that found in chronic altitude acclimatization. Most of our subjects had a respiratory alkalosis but although hypoxia increased as arterial oxygen saturation fell on exercise, there was little evidence of increased hyperventilation as judged by a fall in $Paco_2$ or increase in ventilation equivalent. Only 2 patients showed marked increase in ventilation on maximum exercise. Both had low arterial oxygen saturations at the time. It seemed that although most of our patients had resting saturations over 90 per cent, they were acclimatized to hypoxia in the sense of responding little to increasing arterial hypoxia.

The results of pulmonary function tests are difficult to evaluate in children because of the relatively wide range of normal values. Many of our patients seemed to have reduced vital capacities and large residual volumes when compared to predicted normal values based on height and weight. These findings may have been due partly to the previous thoracotomy. However, the highest pulmonary vascular pressures and flows were associated with the most abnormal lung volumes (Fig. 3), and in 2 cases there was also evidence of maldistribution of inspired air. Residual volume was increased in patients with increased wedge pressure. Previous reports have noted that pulmonary congestion, particularly in mitral valve disease with an increased left atrial pressure,[28-30] may be associated with a normal or small vital capacity and an increased residual volume. Our results seem to extend these observations to include pulmonary congestion

resulting from an acquired left to-right shunt While the cause of these abnormal lung volumes is still in doubt some recent observations on the effect of pulmonary congestion on pulmonary function may be pertinent.[31]

The diffusing capacity for carbon mon oxide in our patients was normal or slightly elevated Any increase presumably developed as a result of the creation of a left to-right shunt and was acquired rather than congenital The reported values for diffusing capacities in patients with con gen tal left to-right shunts are higher than those in our patients although the pulmonary flows were probably similar in the two groups.[33-34] It seems reasonable to conclude that the normal or only slightly elevated diffusing capacities found in our study resulted from a combination of the opposing factors of pulmonary vascular distension and a congenitally restricted pulmonary vascular bed

Summary

We report the results of hemodynamic exercise and pulmonary function studies in a group of patients with Fallot s tetral ogy and an aortopulmonary shunt of more than 5 years duration. None of the patients had developed severe pulmonary hyper tension or histological evidence of pul monary vascular disease. Exercise toler ance was always limited usually by tiredness in the legs rather than dyspnea. The patients with the largest pulmonary flows and pressures had the least drop in arterial oxygen saturation when they were stand ing and were able to work at the largest loads.

The effect of high pulmonary blood flow and pulmonary venous congestion on the lung volumes was simila to that produced by pul onary congestion n other diseases.

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Mechanisms of onset and termination of abnormal cardiac rhythm studied by constant monitoring

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Knowledge of the events which take place at the onset and termination of the cardiac arrhythmias has been useful in understanding the mechanisms of the arrhythmias in experimental animals as shown by Moe, Harris, and Wiggers. Information concerning the onset and termination of abnormal rhythm in man is scarce, being dependent on chance observations or recordings. Since such knowledge might throw light on the factors at the beginning or end of arrhythmias which could help either in understanding the underlying mechanism or in treatment it was decided to obtain this information by constant monitoring of the electrocardiogram and computed heart rate with special attention to the sequences occurring at the onset and termination of attacks in man. The method is specially adaptable to a study of the paroxysmal arrhythmias and of rhythm disturbances that are terminated with drugs.

Methods

Facilities for monitoring consisted of a mobile, two-channel magnetic tape recorder and a recording cardiotachometer as shown in Fig 1. The latter instrument permitted a 24 hour count of premature beats and proved a useful aid in searching the tape for conversion sequences. Patients were monitored while resting in bed or sitting in a chair. Wires were attached to the chest by snap fasteners† crimped to adhesive patches.‡ The exposed flat under side of the fastener served as the electrode and was smeared with a nonirritating electrode jelly.§ Two bipolar chest leads were used of which one augmented T waves and reduced R wave amplitude and the other produced a tall R wave to trigger the cardiotachometer. The first of these leads connected the left side of the manubrium to the fourth rib along the right sternal border; the second lead employed the same manubrial connection and a

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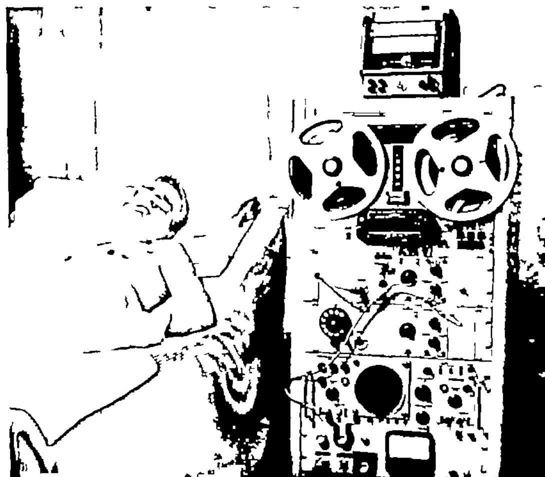


Fig 1 The t o-channel mobile tape recorder and recording cardiotachometer as used at th bedside Using recording speed of 15/16 /sec. provides 16 hours of uninterrupted recording on tape. The frequency of premat re be ts is recorded on the trip chart recorder continuously for 28 hou period. The t lephone dial permit coding the tape with patient st dy number time nd type of drug being used on the magnetic tape

connection near the cardiac apex. A ground wire was attached over the xiphoid process.

Patients selected were those who gave a history of a paroxysmal arrhythmia or who were undergoing medical conversion of an arrhythmia There were 137 patients monitored for periods generally of a week s duration but only those providing useful data are reported here

The results in 17 monitored patients with atrial flutter treated with digitalis are shown in Fig 2 In the 10 patients who converted to atrial fibrillation the atrial rate increased from a mean of 271 4 ± 11 4 (S E.) to 300 ± 15 7 beats per minute Four of these patients terminated with normal sinus rhythm In the 7 patients who remained in atrial flutter after digitalis therapy the atrial rate increased from a mean of 266 6 ± 9 to 279 ± 16.1 beats per minute. The mean increase in atrial rate in the patients terminating with atrial fibrillation was 24 6 ± 2 7 beats per minute compared with 12 6 ± 10 beats per minute for those patients whose atrial flutter failed to terminate. Using the t test for paired observations, the atrial rate change in the successful terminations was significant ($P < 0.001$) and in the unsuccessful terminations was not significant ($P = 0.25$)

These results show that the conversion of atrial flutter to atrial fibrillation is correlated with the ability of digitalis to increase atrial rate This desired action is dependent on the greater relative magnitude of the indirect vagal action of digi

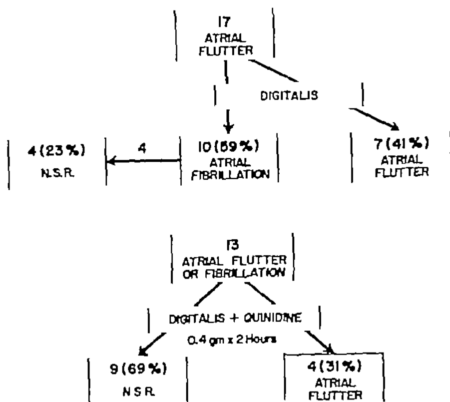


Fig. 2. Of 18 patients with atrial flutter or fibrillation, 14 (78 per cent) converted to N.S.R. with digitalis or the combination of digitalis and quinidine.

talis, as suggested by Farah and Loomis. Thus the present studies confirm that the overriding effect of digitalis in man is vagal—except for 2 patients in whom the direct muscular effect of the drug caused a slowing of the atrial rate and in two patients in whom the drug caused no change in atrial rate. This tendency for the direct action of digitalis to occasionally override or balance the vagal action prevents effective use of the drug in terminating atrial flutter in many patients.

The transition from atrial flutter to atrial fibrillation was an uneventful gradual increase in atrial rate until the atrial rhythm became irregular. It is of interest that postconversion interference dissociation was not observed in the 4 patients who terminated with normal rhythm nor in 4 additional patients in whom atrial flutter terminated without drugs. In these studies postconversion interference dissociation was observed only after the combined use of digitalis and quinidine.

Combined use of digitalis and quinidine

The patients with atrial flutter who failed to convert to a normal sinus mechanism with digitalis were given quinidine 0.4 Gm. every 2 hours for up to 8 doses. Quinidine in these doses caused a slowing in the atrial rate from a mean of 257 ± 4.4 to 199.1 ± 17.8 beats per minute in those instances where the rhythm terminated with normal sinus rhythm. When quinidine therapy was unsuccessful in terminating the rhythm the atrial rate still slowed from a mean of 256.3 ± 14.6 to 201.8 ± 16.4 beats per minute. The mean decrease in atrial rate in the 7 successful instances was 57.9 ± 15 beats per minute which was a significant change ($P < 0.01$) compared with 55 ± 21.5 beats per minute in the 4 unsuccessful cases. However, the magnitude of the quinidine-induced atrial slowing does not differ significantly in the successful compared to the unsuccessfully treated groups. This indicates the futility

of attempting to predict which patients will convert to normal sinus rhythm by monitoring atrial rate. It is also apparent that some other factor than mere atrial slowing accounts for the termination of atrial flutter by quinidine.

Since all patients in this group were fully digitalized in addition to receiving quinidine it was not surprising to find more than one mechanism of termination. In 9 patients, the quinidine effect was pre dominant so that progressive slowing of the atrial rate occurred When the atrial rate was reduced below 176 2 patients exhibited asystole lasting 1 3 and 2 5 seconds respectively (as shown in Fig 3) and 2 patients exhibited interference dissociation followed by normal sinus rhythm in each case Three patients whose atrial rate declined but failed to fall below 176 remained in atrial flutter In 4 patients, the atrial rate fell initially but remained between ?14 to ?73 or actually increased suggesting an overriding digitalis effect all developed atrial fibrillation followed by normal sinus rhythm in three Of the 7 atrial flutter patients terminating with normal sinus rhythm 3 developed a post conversion interference dissociation

The spontaneous termination of atrial flutter occurred in circumstances that produced a slowing of the atrial rate followed by a short period of asystole in 3 patients. This was similar to the effects observed with the use of quinidine. The period of asystole lasted from 1 to 2 4 seconds before normal sinus rhythm was resumed as shown in Fig 3 Since quinidine slowed the atrial rate in flutter producing asystole and a similar mechanism was observed in 3 patients during the spontaneous termi nation of atrial flutter this suggests that a brief period of asystole is not a toxic effect of quinidine.

Two additional patients monitored dur ing the spontaneous termination of atrial flutter showed no atrial slowing and de veloped atrial fibrillation instead of asy tole followed by a normal sinus mechanism

The opportunity to record the onset of atrial flutter is rare and this event has been monitored in only 4 patients. One of these was a 2½ week old infant with paroxysmal atrial flutter and fibrillation in whom 381 transient attacks of atrial fibril lation and 75 transient attacks of atrial flutter were monitored In addition to studying the time of onset of each of these attacks, the time of appearance of 437 atrial premature beats was noted with respect to the onset of the last normal P wave Tracings on this patient printed

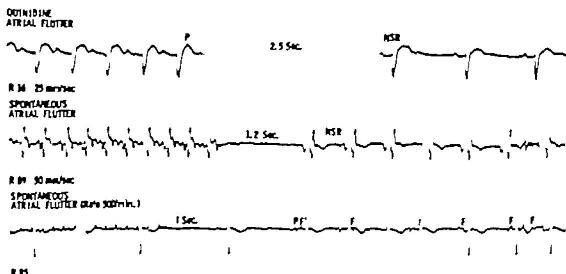


Fig 3 Termination of atrial flutter (upper trace) with quinidine is followed by electrical pause which is similar in magnitude to the pause occurring following spontaneous termination of atrial flutter (lower 2 traces) and has a range of 1 to 2.5 sec in both situations.

from magnetic tape are shown in Fig 4 The frequency of attacks of both atrial fibrillation and atrial flutter and atrial premature beats occurring at various times after the last normal P wave, are shown in Fig 5 It was immediately apparent that the onset of neither atrial fibrillation, atrial flutter nor atrial premature beats fell at random in the electrical cycle. The mean time of onset of atrial fibrillation occurred 139 9 ± 35 (S.D) msec. after the last normal P wave atrial flutter began 174.5 ± 39 4 msec. after the last normal P wave and the mean time of onset of atrial premature beats was ?21.3 ± 65 msec after the last normal P wave The difference

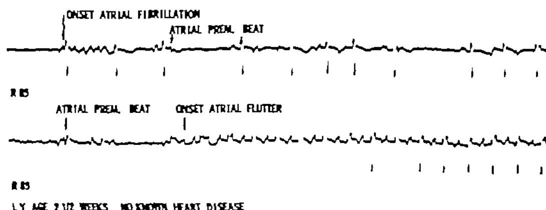


Fig 4 The onset of atrial fibrillation is shown occurring in the P S interval in the upper trace The lower trace shows the onset of atrial flutter occurring in the S-T interval. Several atrial premature beats are shown.

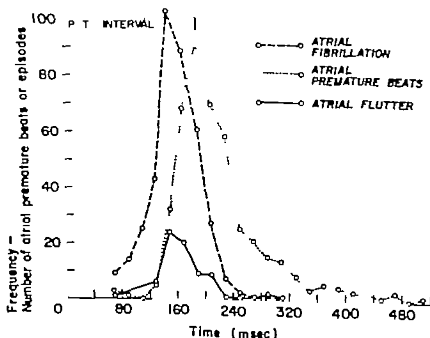


Fig 5 The frequency of atrial premature beats, atrial flutter and fibrillation are plotted according to the time of onset after the last normal P wave Since large numbers of premature beats and episodes of arrhythmia were plotted, these were grouped and the midpoint of each group considered as the time of onset. Thus the group plotted as 70 msec. corresponds to time of onset from 60 to 80 msec after the normal P wave.

between the mean time of onset of both *atrial fibrillation and atrial flutter compared* to the mean time of onset of atrial premature beats is significant ($p > 0.001$)

These observations suggest a coupling mechanism to the previous atrial cycle for atrial premature beats, atrial flutter and fibrillation. Since the attacks of atrial flutter and fibrillation occurred earlier in the electrical cycle than did atrial premature beats, the duration of the atrial T wave was measured to see if this separation could be explained by incomplete atrial recovery favoring the development of either atrial flutter or atrial fibrillation. The duration of the atrial T wave was measured in blocked atrial premature beats where the atrial T wave could be seen separated from the QRS complex. The mean duration of the atrial P T interval was 190 msec which meant that the majority of attacks of atrial flutter and fibrillation began before atrial recovery was complete and the majority of atrial premature beats occurred after recovery was completed. The fact that the onset of atrial flutter and fibrillation favors a time in the electrical cycle when the atria *are incompletely recovered would favor* reentry as the underlying mechanism. Most investigators have stated assumed or implied that fibrillation results from early premature responses in partially or irregularly excitable tissues. The significance of depression of conduction velocity in the initiation of fibrillation which occurs with propagation of electrical impulses in the relatively refractory period is specifically considered by Moe Harris and Wiggers[1] and Moe and Méndez. Moe and Abildskov[4] have reinvestigated the mechanisms of fibrillation and although unwilling to attribute fibrillation to a single mechanism these authors suggest that nonuniform recovery of atrial muscle with the accompanying slow conduction velocity in relatively refractory muscle favors formation of wavelets which lead to sustained atrial fibrillation.

Atrial premature beats occurring after atrial recovery is completed are simply propagated over the atrium leaving no further pathway for reentry. Atrial premature beats were seen in all parts of the electrical cycle but the greatest frequency occurred toward the end and immediately *following the atrial T wave. The mechanism* of this obvious tendency for atrial coupling is not explained by these studies, although a single reentrant path is the hypothesis favored by the data presented rather than the random occurrence of ectopic beats. Wallace and Mignone[4] have explained ventricular coupling on the basis of a reentrant pathway produced artificially by local myocardial cooling and the mechanism for atrial coupling is probably related to reentry also.

Atrial and nodal tachycardia

Paroxysmal atrial and nodal tachycardia began with one or more premature beats occurring in an irregular sequence. When more than one premature beat preceded the stable tachycardia the ectopic rate either accelerated or decelerated varying during the onset as much as 37 beats per minute before a stable rate was achieved. There was no constant relationship between the timing of the first premature beat and the previous cycle. Study of single attacks in 8 patients revealed that the initial premature beat fell after the *previous T wave in 5 in the previous S-T* interval in 2 and in the previous T S interval in 1.

Examples recorded from three patients are shown in Fig 6. The upper two tracings show decelerating ectopic rates before a stable tachycardia is achieved. In the second tracing the first atrial premature beat appears at the apex of the previous T wave and in the subsequent cycles on the upstroke of the T wave.

When more than one attack could be recorded in the same patient the same complex sequence of ectopic activity was occasionally observed during each subsequent attack. An example of this is shown in Fig 6 (2 lower tracings) where 2 attacks of nodal tachycardia are preceded by trigeminal rhythm made up of a normal and 2 nodal ectopic beats with interference dissociation. Notice that in each attack the equivalent rate of the second pair of nodal beats is slower than the first pair. Following this a nodal beat falls on the previous T wave. Then there is an accelerating rate of nodal ectopic activity with retrograde conduction show

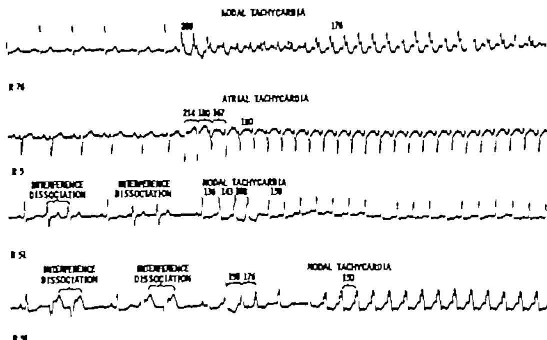


Fig. 6 Recordings of the onset of atrial and nodal tachycardia showing the decelerating rates of premature beat activity in the upper 2 traces The lower two traces are from separate attacks in the same patient, showing remarkably similar and complex premature beat activity See text for description

ing progressive retrograde block. In the third tracing the attack begins with a stable rate of 150 while in the lower attack marked retrograde block occurs with the P wave falling after the T wave. The attack begins with normal conduction becoming progressively aberrant over the next 3 beats. A stable tachycardia of 150 per minute then ensues.

The period of most conspicuous variation in rate during atrial and nodal tachycardia was observed toward the end of attacks when the atrial rate slowed an average of 23 ± 3.3 beats per minute in 13 patients, as shown in Fig 7 Two patients were excluded from this study one had nodal tachycardia superimposed on atrial fibrillation and in one the tape was accidentally erased. Two of the patients included in the analysis showed the characteristic abrupt termination which is considered the usual method of termination in textbooks. In these 2 patients the atrial rate slowed only 4 and 5 beats per minute respectively before the rhythm terminated The data presented here suggest that gradual termination is the more usual method of termination.

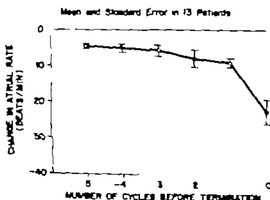


Fig 7 The changes in rate between the last cycle of the tachycardia and the fifth cycle before termination is highly significant ($P < 0.00001$) and for the next to last and final cycle ($P < 0.001$)

Termination of the attack was followed by sinus pause lasting from 0 9 to 5 6 seconds in 9 of 14 patients, during which time ventricular escape in the form of single multiple or coupled ventricular beats was observed in 10 of 14 patients. The ventricular rate during this escape activity exceeded the attack rate by a

wide margin in 3 patients, as shown in Fig 8 *In the upper trace after slowing* of atrial rate occurs the attack appears to be interrupted by two paired ventricular beats with an equivalent rate of 250 per minute compared to the attack rate of 214 per minute. The 2 middle tracings are from patients with nodal tachycardia treated with a pressor agent Short bursts resembling ventricular tachycardia occurred during the usual pause and this was not observed with any other form of therapy This result is attributed to raising pressure and not to the specific drug used Similar effects have been reported for epinephrine by Levy and Allen[7] and for norepinephrine by Meek and Conway

When atrial tachycardia with block is treated with digitalis atrial slowing is observed before termination occurs. This effect is of course the opposite to that expected in atrial flutter where after digitalis, the atrial rate increases before *terminating with atrial fibrillation* It is of interest that in one patient monitored during the digitalis-induced termination of atrial tachycardia with block atrial slowing was followed by several sudden increases in atrial rate until during one of these the rhythm terminated as shown in Fig 9 Thus, digitalis initially slows the atrial rate, but it is possible that as the dose of digitalis is raised a different mechanism similar to that seen in atrial flutter takes over

Summary

Digitalis accelerated the rate in atrial flutter resulting in atrial fibrillation whereas the addition of quinidine slowed the atrial rate producing either asystole or interference dissociation In some patients receiving both digitalis and quinidine the atrial rate showed less of a tendency to slow or actually increased resulting in

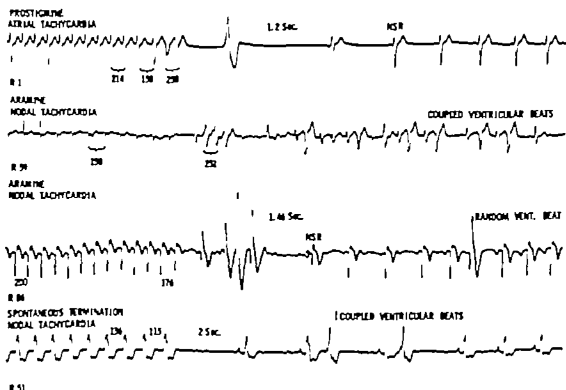
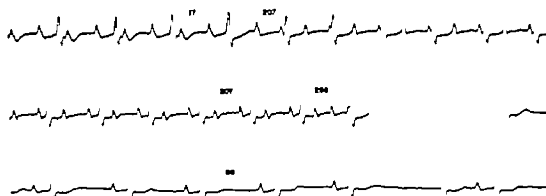


Fig 8 The offset of atrial and nodal tachycardia recorded in 4 patients showing the 3 types of ventricular escape i.e., paired beat (upper trace) short burst of ventricular tachycardia (the middle traces) and coupled beat (lower trace). The characteristic slowing of the rate as the attack subsides is best seen in the lower trace All attacks are followed by short period of atrial arrest.



ZOLL AGE 57 RHD – RECEIVING DIGITALIS R 130

Fig 9 The termination of trial tachycardia with 2 1 block by digitalis is haracterized by progressiv slowing of the trial te from 214 to 170 over period of 4 days followed by 3 abrupt increases the trial t which terminated with sinus pause nodal beat nd normal rhythm as shown here.

atrial fibrillation followed by normal sinus rhythm This suggests an overrid ng effect of digitalis.

Since the spontaneous term nation of atrial flutter occurred n unknown circumstances that usually slowed the atrial rate and asystole was observed this suggests that asystole is not a toxic effect of qu ni-d ne

Atrial flutter fibrillation and atrial premature beats began more commonly in the P T cycle than in the T P cycle. Since atrial recovery is more l kely incomplete during the P T cycle this favors reentry as the underlying mechanism n the patient studied

Atrial and nodal tachycardia begin with an irregular sequence of premature beats before a stable tachycardia is established There is usually a significant slowing of the rate prior to termination of the abnormal h thm. Sinus arrest w th ventricular escape is the usual method of terminat on regardless of the form of therapy used Bursts of rapid ventricular rhythm resembl ng ventricular tachycardia were seen only after the use of pressor agents.

Atrial tachycardia with block treated with digitalis show an in tial atrial slowing but as the dose of digitalis was raised in one patient abrupt increases in trial rat occurred unt l the hythm terminated This is a mechanism similar to that seen in the digitalis- nduced termination of atrial flutter

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Gas gangrene of the heart in clostridial septicemia

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Gas gangrene of skeletal muscle is a well recognized entity which occurs most often after trauma. Less well appreciated is gas gangrene of cardiac muscle. Among 3,039 autopsies recorded at the Clinical Center from 1953 through July 1966, histologic evidence of clostridial infection was present in 28 of them. Although *Clostridia* species were cultured from the blood of all 28 patients, either before or after death, the infection was limited histologically to only one organ or tissue in 11, and it was widespread, involving many organs and tissues, in 17. In none of the 11 patients with local (one organ) clostridial infection was the heart involved, but the heart showed histologic evidence of clostridial infection in 9 of the 17 subjects with multiorgan involvement. This report summarizes the clinical and pathologic features in these 9 patients with clostridial cardiac lesions.

Patients studied

The clinical and pathologic features in these 9 patients are tabulated in Table I. Each patient received antineoplastic agents and/or steroids, and all received antibiotics. In 7 of the 9 patients there was evidence, although often only in retrospect, of clostridial septicemia during the last several hours of life. The clinical features consistent with clostridial septicemia in these patients included a fairly sudden elevation of the temperature, tachycardia out of proportion to the fever, a fall in blood pressure, dyspnea, occasionally jaundice, and irritability in the face of an alert sensorium. Only one (F. P.) of the 9 patients studied had an ECG during the final 24 hours. It was recorded 6 hours before death while he was febrile (40.2° C.), normotensive, and apprehensive, but alert. It showed ventricular tachycardia (rate 200 per minute). This man's hemoglobin level dropped from 10 to 8 Gm. per 100 ml. during the final 6 hours, and blood cultures drawn during this period grew *C. perfringens*.

The time intervals between death and autopsy ranged from 2 to 16 hours (average, 9 hours). The heart was of normal size in every patient, but in each the myocardium was soft, flabby, dark brown, and occasionally crepitant (Fig. 1). The endocardium and the intima of the blood vessels, especially the large ones, were stained pink in 8 of the 9 patients (Fig. 2). Sections of myocardium of each of the 9 patients contained focal extravascular collections

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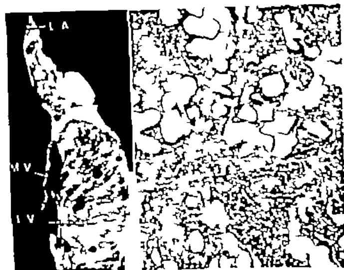


Fig. *1* Gas cysts in the myocardial wall of patient G. B. (A59-145). Left, A cut section of left atrium (*L.A.*), atrioventricular sulcus, posterior leaflet of mitral valve (*M.V.*), and left ventricle (*L.V.*) is shown. Numerous gas cysts are present in the myocardial walls of both atria and ventricles as well as in the adipose tissue of the A-V sulcus. Right, Photomicrograph of section of left ventricular myocardium demonstrating the numerous gas cysts. (Hematoxylin and eosin stain. ×14.)

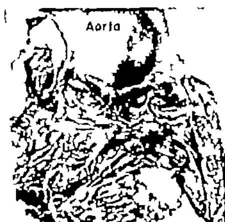


Fig. *2* Opened left ventricle (*L.V.*), aortic valve (*A.V.*), and aorta in patient K. I. (A65-141). There is severe reddish staining of the intima of the aorta, the endocardium of the aortic valve, and anterior mitral leaflet (*A*). This staining is the result of intravascular hemolysis which is characteristic of clostridial septicemia.

of relatively large, gram positive rods consistent with clostridium species (Fig. 3 to 5) and in all but 1 patient (F. P.) these interstitial organisms were present in abundance. Foci of degenerated myocardial fibers separated from one another by interstitial fluid were present in the regions of large focal collections of organisms. The organisms were often attached to the margins of the fragmented muscle fibers, but did not invade them. No inflammatory cells were present in the myocardium. In several patients, collections of clostridial organisms also were present in the subepicardial adipose tissue of the atrioventricular sulci and some of the fat cells in such areas were necrotic. In several patients small intramural coronary arteries contained clostridial organisms in their lumina, and an occasional vessel appeared to be obstructed by them. Lymphatic channels in the subepicardial adipose tissue in 3 patients contained clostridial organisms and clumps of degenerated myocardial fibers. Gas bubbles or cysts, sometimes lined by clostridial organisms (Fig. 4) were present in the myocardium of all 9 patients. In each of the 9 patients there were, in addition, other nonspecific myocardial changes generally indicative of a systemic infection. These changes consisted principally of cloudiness and increased eosinophilia of the fibers without loss of cross-striations.

Comments

Although none of the patients in this study had underlying cardiac disease, the

Table I. Clinical and pathologic data in the 9 patients with gas gangrene of the heart

Patient	Age	Sex	Primary diagnosis	Species of Clostridium
1. A. S. A55-31	36	M	Acute leukemia	*Perfringens*
2. F. I. A56-3	42	M	Acute leukemia	*Perfringens*
3. W. C. A56-42	59	M	Chronic leukemia	*Septicum*
4. G. B. A59-145	54	M	Hemochromatosis	*Perfringens*†
5. T. M. A59-177	23	M	Malignant melanoma	Not specified
6. A. F. A59-185	43	F	Acute leukemia	*Perfringens*†
7. P. W. A60-241	15	M	Hepatitis	Not specified†
8. L. C. A60-259	64	M	Regional enteritis	*Perfringens*†
9. K. I. A65-141	59	M	Waldenstrom macroglobulinemia	*Perfringens*†

*Cultured from blood [illegible] as well as after death.
†Cultured from blood [illegible] necropsy. No blood cultures during last 24 hours.

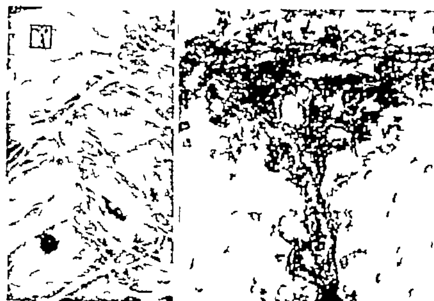


Fig. 3. Clostridial lesions in the myocardium [illegible] of patient T. M. (A59-177). Left, Section of left ventricle. All of the dark areas are collections of clostridial organisms. Right, Close-up of the lesion enclosed in brackets in the left photomicrograph. (Left, hematoxylin and eosin stain, ×22; right, ×315, Brown and Brenn stain, ×315.)

first patient proved to have systemic gas gangrene reported by Welch and Nuttall in 1892 had an aneurysm of the ascending aorta which had perforated by a small opening through the anterior thoracic wall and which had given rise to repeated external hemorrhages.[23] The patient died suddenly and at necropsy there were gaseous cysts within the lumina of most blood vessels and in the pericardial sac, cardiac chambers, myocardial walls, and the intra-aneurysmal thrombus. The subcutaneous tissue of the chest wall contained similar cysts, as did the liver, spleen and kidneys. In each of these organs or tissues the authors found a gas-producing bacillus which they named *Bacillus aerogenes capsulatus*. It is probable that in the initial patient the bacillus gained access to the blood stream by means of the aortic aneurysmal-cutaneous fistula. The authors also described blood stain

Clinical gas of septicemia	*Site of entry of clostridial organism*	*Clostridial myocardial lesion*	*Pink staining of endocardium and intima*	*Time from death to necropsy (hr.)*
+	Colon	+	+	3
+	Colon	+	+	2
+	Small intestine	+	+	13
0	Esophagus	+	+	13
+	Small intestine	+	+	6
0	Small intestine	+	+	11
+	Respiratory tract	+	0	2
+	Small intestine	+	+	16
+	Stomach	+	+	15



Fig. 4. Clostridial infection of myocardium in patient P. W. (A60-41). Left: The myocardial fibers are necrotic and between them are numerous gram-positive bacilli. No inflammatory reaction is present. Right upper: Gaseous cyst lined with clostridial organisms. Right lower: Close-up of area in brackets, showing the lining of the cyst. (Left: hematoxylin and eosin stain, ×100; right upper, ×360; right lower: Brown and Brenn stain, ×1,340.)

ing of the endocardium and intima of blood vessels, a sign which has since become recognized as characteristic of systemic clostridial infection. This staining is believed to result from the rapid intravascular hemolysis which occurs in clostridial septicemia.

The cardiac infection in each of the present patients was secondary to generalized clostridial septicemia with the primary focus being a gastrointestinal or respiratory tract ulcer. Clostridial infection limited to the heart has not been reported although several patients have been described in whom cardiac involvement was the most impressive feature of their ill



Fig. \I l bundle in patient G. B. (459-145). Left. The bundle is outlined by the dashed line (case t presc t a the caudal half of the bundle. Right. Close-up iew of portion of A V bundle show idial orga nms as ll cy ts. No conduction disturbances were detected this patient. (Left h l nd eos -to ×55; right Brow nd Brenn tai ×650.)

Janbon and associates[2] in 1934 described *C. welchii* septicemia with endocarditis or endomyocarditis in 3 patients who had changing murmurs on precordial examinations and evidences of cardiac failure. In none of their patients, however, was a necropsy performed to verify their clinical diagnosis. In 1943 Moore[3] reported autopsy-confirmed *C. welchii* endocarditi of the aort c valve n a 34-year-old woman with rheumatic heart disease and evidence of clostridial infection for 9 weeks. The endocarditis in thi patient followed vaginal insertion of radium for carcinoma of the uterus. Her clostridial abscesses in the leg, kidney, and spleen, which were devoid of gaseous cysts, were interpreted as the result of septic embolization from the aortic vegetations. The clostridial endocarditis appears to have become established in this patient because the bacteremia wa prolonged and the card c valves were previou ly damaged. Tennant and Parks and Korns[7] reported *C. perfringens* infection at the site of an acute myocardial infarct. The clostridi l abscess at the site of the myocardial necrosis n one of these patients caused rupture of tl heart.[7] Aside from the heart, this patient had histologic evidence of clostridial infection only in the gall bladder. Korns' patient had foci of necrotic intestinal mucosa and clostridial organisms were found in the lungs and spleen in addition to the heart.

The hallmark of gas gangrene of skeletal muscle is local pain or a sense of heaviness of the affected part, followed by increasing edema and duskiness.[8] The skin of the involved region becomes tensely swollen and the wound often exudes a thin, dark fluid which contains clostridial organisms and gas bubbles, but few or no inflammatory cells. In none of the patients reported herein were there any clinical signs or symptoms which could be specifically attributed to gas gangrene involving the cardiac muscle. Other manifestations of this extremely toxic and usually lethal infection, however, could obviously have masked any clinical features resulting from the clostridial myocarditis. None of the patients had a significant pericardial ef fu ion nor were the pericardial sacs d tended by gas.

Still unresolved is the specific mecha

nism by which striated muscle becomes cystic and degenerated when infected by clostridial organisms. With reference to skeletal muscle, one postulate is that the blood vessels and capillaries supplying and draining the tissue are damaged and become obstructed with resulting anoxia of the muscle. The anoxic muscle in turn provides a favorable environment for further bacterial multiplication and production of toxin with continuing invasion and destruction of contiguous muscle. A more generally accepted view is that the myonecrosis and gaseous cysts are due directly to the exotoxins and other metabolic products elaborated by the organisms, particularly α-toxin, a lecithinase with potent hemolytic and necrotizing properties.[9] The site of action of the exotoxins within the muscle fibers is presently not known.

In the case of the cardiac muscle it is difficult to attribute the myonecrosis to obstruction of the coronary vessels by colonies of clostridial organisms or gaseous cysts. Although the lumen of an occasional intramural coronary vessel was observed to be filled with organisms in the patients studied here, the process was clearly not extensive enough to account for the widespread myocardial alterations. As with skeletal muscle, it appears more reasonable to believe that the myocardial fibers are damaged directly by the exotoxins elaborated by the clostridial organisms, and that the fibers are subsequently replaced and displaced by the gaseous cysts. During this process some of the partially digested myocardial fibers are apparently embolized to the cardiac lymphatic channels.

One of the cardinal features of clostridial infection of muscle, both skeletal and cardiac, is the scant cellular inflammatory response to the invading organisms. Even when exudation occurs, those cells in the vicinity of the organisms undergo karyolysis and cytolysis. Furthermore, there is no vascular hyperemia or fibrin formation. Specifically because there is no inflammatory reaction the term "myonecrosis" has become recognized as preferable to "myositis" in cases of clostridial infection.

It is not known why some patients with clostridial septicemia have widespread organ involvement as evidenced by focal collections of extravasated organisms with necrosis and gas-cyst formation while other patients develop histologic evidence of infection in only one or none of the organs. Why the heart is involved in some patients with widespread evidence of clostridial infection and not in other patients is also unknown. These differences do not appear to be related to the time intervals between death and autopsy. In the 9 patients with myocardial involvement reported in this study, the postmortem interval averaged 9 hours; in contrast, it averaged 12 hours (range, 2 to 23 hours) in the 7 patients with evidence of widespread clostridial infection but no involvement of the heart. Furthermore, in the 11 patients with histologic evidence of clostridial infection in only one organ, this interval also averaged 9 hours (range, 3 to 15 hours). Carpenter and Wilkens have previously presented other evidence, based on a large autopsy series, that clostridial organisms are not disseminated post mortem during the time intervals involved in this report, although local proliferation certainly cannot be excluded.

Since Clostridia species may be isolated almost wherever sought—foods, clothing, bandages, powders, ointments and operating room air—and are normal inhabitants of the gastrointestinal tract, skin, and vagina, it is somewhat surprising that these infections are infrequent. Ulcerations of the gastrointestinal or genitourinary tracts produced by neoplasms, antineoplastic agents, or irradiation may readily introduce these organisms into the blood stream. Common antitumor drugs along with steroids, multiple antibiotics, and irradiation lower the patient's defensive and immunological mechanisms. In the future when these agents are used even more extensively, clostridial infections will probably become more prevalent.

Summary

Morphologic evidence of invasion of the cardiac muscle was present in 9 out of 17 patients with histologic evidence of widespread systemic clostridial infection. The cardiac lesions consisted of foci of myonecrosis containing numerous organisms, myocardial gaseous cysts, and clumps of

organisms within the lumina of cardiac vascular and lymphatic channels. There was no inflammatory response to the in vading clostridial organisms. Each of the patients with clostridial myonecrosis of the heart had clostridial infection in a number of other organs. The portal of entry was a gastrointestinal or respiratory tract ulceration. It is probable that the incidence of systemic clostridial infections will rise with the increasing use of chemotherapeutic agents steroids and anti biotics.

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Experimental and laboratory reports

The effect of heparin on the heart in anaphylaxis

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Early workers did not recognize the importance of the heart as one of the target organs of anaphylactic shock because the guinea pig heart is seen to beat for quite sometime after all respiratory movements have ceased. It was later demonstrated that in the rabbit the heart is one of the primary sites of anaphylactic shock. The electrocardiographic changes during anaphylaxis in this species are indicative of disturbances in conduction, partial heart block, smooth muscle spasm of the coronary blood vessels, and changes associated with asphyxia.[1]

The entire arterial system of the rabbit undergoes vasoconstriction during anaphylactic shock. It has been suggested recently that a fundamental process in severe anaphylactic shock in the rabbit is the formation of intravascular thrombus, particularly in the pulmonary blood vessels; this can be prevented by pretreatment of the animal with heparin immediately before challenge.

Similar changes may possibly occur in the heart, and in fatal cases coronary thrombosis may be added to coronary vasospasm. It is possible that the thrombotic changes can be prevented by pretreatment with heparin.

The effect of pretreatment with heparin was therefore studied in anaphylactic shock in the rabbit. Electrocardiographic changes were recorded in the animals undergoing anaphylactic shock. The effect of the antigen on contractility, heart rate, and coronary flow was studied in the isolated perfused heart preparation.

In both types of experiments the effect of pretreatment with heparin on the development of anaphylactic symptoms was assessed.

The main experiments were performed in the rabbit. Some experiments were performed in the rat because it has been reported that the abrupt fall in blood pressure during anaphylaxis in the rat may be due to cardiac depression.[4]

Methods

Albino rats of either sex weighing between 100 and 150 grams were obtained from the National Institute of Communicable Diseases, New Delhi. Mongrel rabbits of either sex weighing between 1 and kilograms were purchased from local dealers. The animals were allowed free access to water and were housed in air-conditioned rooms. The rats received "Andiet A" and the rabbits received "Andiet B." The composition of these balanced diets has been reported previously.

The rats were sensitized with 0.5 ml. of horse serum injected intraperitoneally

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and were used 14 to 16 days later for intravenous challenge with 0.25 ml. of horse serum.

The rabbits were sensitized with 6 daily intraperitoneal injections of 1 ml. of 50 per cent egg white in saline; they were used 3 weeks later, either for intravenous challenge with 1 ml. of the antigen solution or after being killed for study of the anaphylactic reaction of the isolated heart.

The electrocardiographic changes were recorded in the classic limb leads by means of a Galileo electrocardiograph. The recordings were taken immediately before challenge and continuously during the injection of the challenging dose as well for the next 15 minutes. In animals which survived beyond this period intermittent records were made for the next 6 hours.

The isolated heart was perfused through the coronary arteries (Langendorff preparation) with Ringer-Locke solution. The contractions were recorded on the smoked drum. The coronary flow was measured and the heart rate counted for 5 minutes, before and after each injection of antigen. Similar readings were then taken every fifth minute for 1 hour or until normalcy was restored.

Results

Studies in the rabbit. In normal control animals, the intravenous injection of the antigen was innocuous; furthermore there was no change in the electrocardiographic record.

Anaphylactic shock was produced by the intravenous injection of a challenging dose in 18 sensitized rabbits. The shock produced was mild in 3 animals and severe in the rest. The results are shown in Table I and Figs. 1 and 2.

The electrocardiographic changes in ani

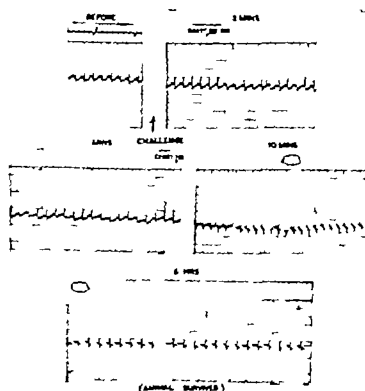


Fig. 1. ECG tracings in mild anaphylactic shock in the rabbit (Lead II). In the control tracing the P is borne in the T wave; rate 254 per minute; normal QRS; T upright. At 3 minutes, rate 278 per minute; depression of S-T segment; upright initial deflection of S wave leading to ...ening of QRS. At 5 minutes rate 265 per minute; depression of S-T segment. At 10 minutes, rate 330 per minute; marked sinus tachycardia; S-T segment isoelectric; P wave borne on T. At 6 hours normal ECG, 240 per minute.

mals undergoing mild shock were transient and normalcy was restored within 6 hours (Fig 1) In animals subjected to severe shock there were marked disturbances in rhythm and conduction with signs of myocardial ischemia (Fig 2)

In another group of 12 sensitized animals heparin (5 000 I U per kilogram) was injected intravenously 30 minutes before challenge as above. In these animals, the shock produced was mild and all of the animals had fully recovered within 6 hours. The electrocardiographic changes were similar to those in the previous set with mild shock, and there was no evidence of coronary infarction in any animal of this group (Table I)

Thus it was seen that injections of heparin afforded considerable protection against anaphylactic shock and prevented myocardial damage ($p > 0.001$)

When the isolated hearts obtained from nonsensitized animals were perfused with Ringer Locke solution the addition of 0 5 ml of egg white solution did not produce any change in tone or contractility There was a reduction of approximately 10 per cent in coronary flow lasting for 4 to 5 minutes after the addition of antigen solution (Table II) It is possible that this transient reduction was due to viscosity of the antigen solution In one experiment the perfusion fluid contained heparin in a concentration of 50 I U per milliliter The effect of the



Fig 2 ECG changes in f tal anaphylactic shock in the rabbit At 4 t 5 minutes after the challenging dose in Lead I the mean deflection re inverted with sharply inverted T wave. The reverse is seen in Lead III The heart rate is 290 per minute, in contrast to 300 per minute before challenge. At 9 to 10 minutes, changes are essentially similar bu in addition there is heart block changing from 2 1 to 3 1 The heart rat varies from 70 to 100 per minute At 14 t 15 minutes, the S-T segment is depressed in Lead I and elevated in Lead II The heart block is persisten ith occasional prem ture beats the heart rate being 85 per minute

Table I

P etreatment	Cl ic l mptom	T pe of hock	Incidence (%)	Characteristic ECG ha ges
Sensitized rab (18 mal)	H rried respiration progres- kness occasional conv l m recovers in 2 t 3 hours mplet ly recov ered w th 24 hours	Mild	16 7	Immediat reduction in heart rate followed by lnu tachy cardia At the height of sinus tachycardia, widening of QRS complex. Changes in S-T segment indicatl of ex haustion of bundle or tra nent spasm of arteries
	H rried piration, repeated n lsions passage of ol and urine cessation of respir tion earlier tha t ppage of heart, death thin 20 m nutes t 2 hours	Severe	83 3	Progressive reduction in heart rat changing pacemaker trial fibrillation, in some nimals trioventricular block entricular extrasys toles hanges in S-T segment suggestive of cardiac ischemia
Sen zed l pre ed h hepa l t h lk ge l m	R piration hurried. Marked eakness. N convulsions. Ultimat recovery in 4 hours	Mild	100	Bradycardia followed by tachy cardia, widening of QRS complex, transient sagging of S-T segment Normal record than 6 hours

addition of egg white solution was similar to that noted above (Table II)

When imilar experiments were per formed with heart ol tained from sensitized anima s the addition of 0 5 ml of 50 per cent egg white solution led to marked al terations in contractility reduction in heart rate and marked reduction in coronary flow (T ble II) The reduction in coronary flow la t d for 15 to 20 minutes. When heparin (50 I U per milliliter) was present in the perfusion fluid in similar experiments performed with heart from sensitized ani mal the addition of antigen to the per fus on fluid produced similar effects (Table II)

Studies in the at In a group of 14 sen i tized anima 2 animal died in anaphy lactic shock w thin hours of challenge Another grou of 13 sen tized animal re- cei d heparin intravenously n a dose of *5 000 I U per kil gram of body weight On* chal nge anim l died within hours Tl el ctrocardiograp c chan es were milar in both gr ups and cons ted f nitial bra lycardia followed by pers tent tachycardia. Thus it was seen that in contrast to the results obtained in the rabbit, pretreatment with heparin aggra vated anaphylactic shock.

When the isolated heart was perfused through the coronary arteries the addition of antigen (0 25 ml of horse serum) to the perfusing fluid led to a slight reduction in coronary flow The reduction in coronary flow and heart rate was marked when antigen was added to the fluid used to perfuse the hearts ol tained from sensitized animals. With heparin (50 I U per milli liter) present in the perfusion fluid similar but less intense effects were pro- duced (Table III)

Discussion

It ha been suggested before that there i a generalized spasm of arteries of the *ral bit during anaphylactic hock. A sp sm* of the coronary artery ha now been demon str ted in both in vivo and in vitro experi ment The sp sm in in vitro experiment with the isol ted heart subsided within 0

Table II. Effect of antigen (50 per cent egg-white solution in saline) on rate and coronary flow in isolated rabbit heart (control or sensitized) perfused by Langendorff method*

Type	Perfusion fluid (temp. 37° C.)	Heart rate (per min.)			Coronary flow (ml./min.)			Effect of contractility
		Before	After	Per cent change (approx.)	Before	After	Per cent change (approx.)	
Control	Ringer-Locke	184	180	−2	19.0	17.0	−10	No effect
Control	Ringer-Locke and heparin	164	160	−2	5.0	4.0	−20	No effect
Control	Ringer-Locke and heparin	100	96	−4	6.0	4.1	−33	No effect
Sensitized	Ringer-Locke	108	80	−26	15.0	3.0	−80	Amplitude increased. Diastolic tone decreased
Sensitized	Ringer-Locke	118	10	−92	4.0	1.0	−73	Mild systolic arrest without recovery
Sensitized	Ringer-Locke	160	120	−25	20.0	10.0	−50	Rise in diastolic tone and amplitude
Sensitized	Ringer-Locke	164	139	−15	21.0	13.0	−38	Rise in diastolic tone and amplitude
Sensitized	Ringer-Locke	112	79	−29	7.0	1.0	−86	Transient mid-systolic arrest
Sensitized	Ringer-Locke	120	84	−30	11.5	6.0	−48	Every fourth beat missing. Atrial contraction not followed by ventricular contraction
Sensitized	Ringer-Locke and heparin	160	132	−18	18.0	10.0	−44	Slight rise in diastolic tone

*See text for method of sensitization.

to 30 minutes, and there was no permanent damage. Since the perfusion fluid was Ringer-Locke's, there was no possibility of thrombus formation. In the in vivo experiments, there was transient spasm without permanent cardiac damage in animals undergoing mild anaphylactic shock. In severe cases it seems to be probable that thrombus formation perpetuated cardiac ischemia. Heparin because of its well-known anticoagulant properties might have prevented this change. This may be one of the factors responsible for the protective action of heparin in anaphylaxis in this species, although it is possible that heparin may have an antianaphylactic action of its own. As expected there was no action of heparin on the isolated heart.

In rats heparin aggravated the intensity of anaphylactic shock but did not modify the ECG changes. It is known that hemorrhage is a characteristic feature of anaphylactic shock in the rat responsible for fatal results and as such aggravation by a potent anticoagulant is not surprising.

In the isolated heart the addition of antigen caused bradycardia and a reduction of coronary flow. In the presence of heparin these changes were consistently less marked. It seems to be possible that more than one mechanism of action of heparin is involved. It may aggravate anaphylactic shock in the rat because of its anticoagulant action and may also possess direct antianaphylactic action.

In the guinea pig asphyxia accounts for fatal anaphylactic shock, but recently it has been reported[14] that, when the spasm of bronchial muscles is prevented by antihistaminic drugs, there is heart failure due to anaphylactic constriction of pulmonary blood vessels, as is characteristically seen in the rabbit.

It is interesting to note that the ECG

*Table III Effec of antigen (horse serum) on rate and coronary flow in isolated rat heart (con trol or sensitized) perfused by Langendorff method**

Type	Perfusion fluid (temp 37°C)	Heart rate (per min)			Coronary flow (ml/min)			Effect on tractility
		Before	After	Per cent change (approx.)	Before	After	Per cent change (approx)	
Control	Ringer Lock	92	99	+ 7	4 0	3 5	−12	No change in contractil ty
Control	Ringer Locke	60	52	−13	3 5	2 8	−34	
Control	Ringer Lock	100	98	− 2	4 0	3 5	−12	
Control	R nger Locke	105	108	+ 3	4 0	3 5	−12	
Control	Ringer Lock	120	125	+ 4	8 0	7 5	− 6	
Control	Ringer Lock nd hepari	52	48	+ 8	1 0	1 0	± 0	
Sensitized	Ringer Lock	140	75	−46	4 6	0 3	−93	Ampl tude of contraction reduced
Sensitized	R ge Locke	110	60	−45	3 0	0 3	−90	
Sensitized	R nger Locke	116	90	−22	3 5	0 5	−86	
Sensitized	R nger Locke	105	55	−48	3 0	0 5	−83	
Sens ized	R ger Locke	109	65	−37	3 5	1 5	−57	
Sens tized	Ringer-Lock nd heparin	74	42	−43	1 9	1 2	−37	Amplit de of contraction reduced
Sens ized	Ringer Locke and heparin	78	34	−56	2 0	1 0	−50	
Sens tized	Ringer Lock nd heparin	142	95	−33	3 4	1 8	−47	
Sens tized	Ringer Lock and heparin	90	95	+ 6	6 0	5 0	−17	
Sensitized	Ringer Lock and hepari	100	95	+ 5	5 0	4 0	−20	

*See text for method of sensitization

changes n man during anaphylactic shock as in severe cases in rabbits consist of cardiac arrhythmia heart block bundle branch block and patterns of acute myocardial ischemia [12]

Summary

The electrocardiographic changes in the rabbit heart during severe anaphylactic shock are indicative of di turbances in function and coronary infarction Pre treatment with heparin reduces the intensity of anaphylactic shock and also modifies the electrocardiographic changes, which then resemble patterns seen in mild non fatal shock.

In the rat heparin increases the severity of anaphylactic shock The importance of coronary thrombus formation in determin ing fatal outcome in anaphylaxis in the rabbit has been emphasized and the find ings have been discussed in the light of current knowledge.

The tech ical assistance of M D N Sharma nd M S L Kapoor is gratef lly acknowledged.

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Diagnosis of experimental intraoperative myocardial infarction by measurement of certain enzymes

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The diagnostic efficacy of measurement of the serum levels of glutamic oxaloacetic acid transaminase (GOT), total lactic dehydrogenase (LDH), heat-stable LDH (LDH) and other enzymes as a means of detecting the presence of an acute myocardial infarction has been established during the past decade and a half.[illegible] These tests for serum enzyme elevation are usually valid for the detection of an acute myocardial infarct which occurs in an otherwise healthy individual. The elevation of the serum values of certain of these enzymes occurs during the early postoperative period in the absence of myocardial infarction; therefore, tests for serum enzyme elevation often give confusing or inconclusive data in regard to the detection of a myocardial infarction which occurs intraoperatively or during the early postoperative period. The present study was undertaken to evaluate the validity of monitoring the postoperative serum levels of GOT, total LDH, and LDH in order to diagnose experimentally produced intraoperative myocardial infarcts.

Methods

Mongrel dogs were used in these studies. The animals were separated into 5 groups according to the operative procedure to be performed. Intravenous pentobarbital anesthetization was used routinely; mechanical endotracheal ventilation was used in those animals that were subjected to thoracotomy.

The animals in Group 1 were subjected to laparotomy and the injection of Angio-Conray (80 per cent solution of sodium iothalamate) in a dose of 1 c.c. per kilogram of body weight directly into the inferior mesenteric artery. The animals in Group 2 were subjected to laparotomy and the creation of a Roux-en-Y jejunostomy limb of approximately 18 inches in length. A cutaneous stoma was fashioned by suturing the free end of the jejunostomy limb to the skin of the abdominal wall. The dogs in Group 3 mock ligation of a coronary artery was performed. A left anterior thoracotomy was performed in the fourth intercostal space and the pericardium was opened. The anterior descending branch of the left coronary artery was mobilized from its myocardial bed at a site approximately 2 cm. from the bifurcation of the left coronary artery. The artery was not occluded. In the animals in Group 4, the anterior descending branch of the left coronary

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artery was similarly exposed mobilized from its myocardial bed 4 to 5 cm from the bifurcation of the left coronary artery and then doubly ligated at that point. In the dogs in Group 5 the anterior de scending branch of the left coronary artery was doubly ligated at a point 1 to 2 cm. from the bifurcation of the left coronary artery

The operative wounds were repaired with routine techniques. Expansion of the lung was assured by intrapleural catheter suction after the repair of the thoracotomy wounds. Postoperatively the animals were offered standard kennel rations.

Specimens of blood were procured from each animal preoperatively and on the first and second postoperative days. The serum from each specimen of blood was subjected to quantitative assay for GOT LDH and LDH The determinations of GOT were performed by the method outlined in Sigma Technical Bulletin No 505 The GOT values are expressed in Sigma Frankel units per 100 c.c of serum The LDH determinations were performed by the method outlined in Sigma Technical Bulletin No 500 LDH determinations were performed by precisely the same method as the total lactic dehydrogenase except that the serum was incubated at 60° C for 15 minutes before the test. The LDH and LDH" values are expressed as Burger Broida units per 100 c.c of serum

The ranges of normal canine serum values of GOT LDH and LDH were determined on the basis of data obtained from apparently healthy normal animals that had not been operated upon The data obtained were subjected to statistical analysis, and frequency-distribution curves were constructed The results served as a basis for estimation of the significance of the postoperative elevations observed

The peak postoperative serum values of GOT LDH and LDH were determined in each animal By appropriate tabulation the relationship of the peak postoperative enzyme values to the range of normal values and to the operation performed was determined in each animal which survived long enough (48 hours) to permit procurement of 2 postoperative specimens.

Results

Seventy-seven animals were operated upon the group distribution and survival are recorded in Table I There was a significant mortality rate (38 per cent) in Group 5 a total of 63 animals survived to undergo the full regimen of enzyme studies.

The ranges of normal GOT LDH and "LDH serum values in the dog were determined on the basis of preoperative serum values in 54 apparently healthy animals. The normal values of GOT ranged from 0 to 34 units with a mean of 12.8 units and statistical analysis of the frequency distribution revealed that one standard deviation (SD) was equivalent to 7.3 units. The normal values of LDH ranged from 0 to 930 units with a mean of 453 7 units and SD of 217 8 units. The normal values of LDH ranged from 0 to 160 units with a mean of 19.3 units, and SD of 32 9 units.

The peak postoperative values of GOT LDH and LDH are tabulated in Figs. 1 to 3 In general, the peak values of each enzyme were greater in the animals subjected to coronary artery ligation than in those not subjected to coronary artery ligation The normal range extends from 0 to a value which is approximately 3 SD above the mean of the preoperative or normal values. The incidences of the appearance of abnormally elevated values of GOT LDH and LDH during the postoperative period are recorded in Table II Abnormally elevated GOT values occurred in 47 per cent of the animals that were not subjected to coronary artery

Table I Group distribution and survival

Group	Animals operated upon	Animals that survived for evaluation
1	10	10
2	10	10
3	10	10
4	10	10
5	37	23
Totals	77	63

Animals that survived beyond hours.

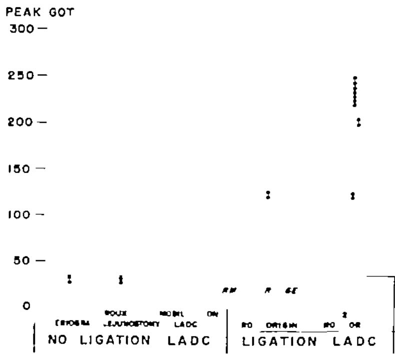


Fig. 1. Peak postoperative ...lues of GOT according t... the operative procedure.

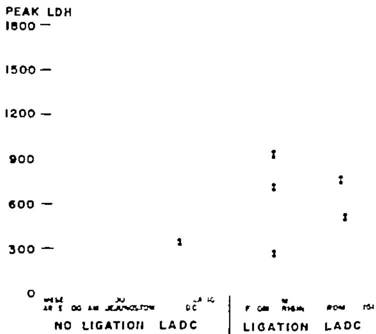


Fig. 2. ...k postoperative ...lues of LDH accord...g t... the operativ... pr...edure.

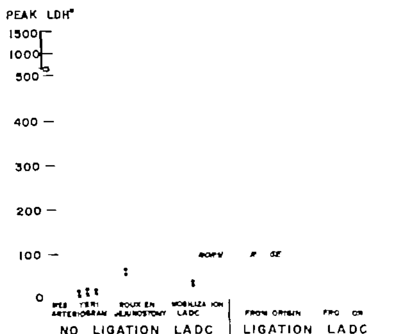


Fig 3 Peak postoperative values of LDH according to operative procedure performed

*Table II Incidence of abnormally elevated enzyme value during postoperative period**

Group	GOT Ratio	GOT Per cent	LDH Ratio	LDH Per cent	LDH" Ratio	LDH" Per cent
1	3/10	30	1 10	10	0 10	0
2	4/10	40	0/10	0	1 10	10
3	7/10	70	0/10	0	1/10	10
4	10 10	100	4 10	40	8 10	80
5	23/23	100	10 23	43	21 23	91

*Values of GOT greater than 35 units, LDH greater than 910 units, and LDH" greater than 73 units are considered abnormally elevated

ligation and in all animals that were subjected to it An abnormally elevated LDH was observed in only one animal that was not subjected to coronary artery ligation and in only a minority of animals that were subjected to it Abnormally elevated LDH" was found in 7 per cent of the animals not subjected to coronary artery ligation and in 88 per cent of the animals that were subjected to it It seems that an elevated serum level of LDH" was more significant than that of GOT or LDH as an indicator of the occurrence of an intraoperative coronary artery occlusion.

The usefulness of the appearance of more extreme elevations of the serum enzymes as an indicator of the occurrence of of myocardial infarction was investigated The validity of using an arbitrary level of postoperative peak values of GOT LDH and "LDH" of up to 10 SD (derived from the frequency distribution of normal values) above the mean of normal values as a test for the occurrence or nonoccurrence of an intraoperative myocardial infarction is depicted in Fig 4 Again the use of a discriminatory value of approximately 3 SD above the mean of normal values as an indicator of the occurrence or nonoccurrence of an intraoperative myocardial infarct is more valid in the case of "LDH" than it is for GOT or LDH However the use of an extremely elevated value of GOT (6 SD above the mean of normal values) seems to be an even more valid indicator (92 per cent accuracy) of the occurrence or nonoccurrence of an intraoperative myocardial infarct That is to

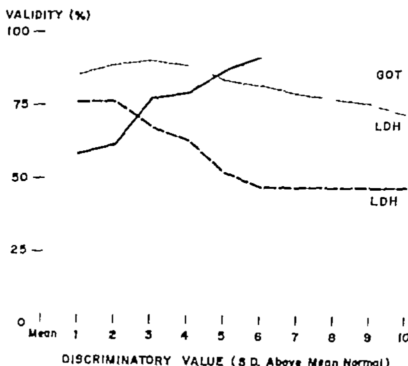


Fig. 4. The validity of utilizing various end-point serum values (standard deviations above mean normal) of GOT, LDH, and LDH as discriminatory tests for the occurrence or nonoccurrence of intraoperative myocardial infarction.

say, the correlation of peak postoperative GOT values greater than 65 units with the occurrence of a myocardial infarct and the correlation of peak postoperative GOT values less than 65 units with the nonoccurrence of a myocardial infarct were valid in 9? per cent of the animals.

Discussion

One inherent problem which is associated with the interpretation of serum GOT values which are observed after a major operative procedure is the postoperative rise of this enzyme which is frequently present in the absence of myocardial infarction.[9, 11] Nickell and Allbritten found that there was frequently a rise of the serum GOT in man after a major operative procedure. A rise of serum levels of GOT is especially likely after operations on the biliary tree or thoracic viscera.[1] In approximately 50 per cent of patients who are subjected to thoracotomy there is a significant postoperative rise of the serum GOT values.[9] Blair and associates[13] found that there was a transient but marked elevation of the serum GOT during the early postthoracotomy period in dogs. They attributed this rise to the thoracotomy per se. In these same animals, coronary artery thrombosis was produced by a delayed technique (requiring no further operative procedure) and there was then a secondary rise of the serum GOT. The initial GOT elevation was often as great as the elevation which was observed after the coronary artery thrombosis.

Lactic dehydrogenases are present in many organs, tissues, and body fluids.[2, 4, 13, 14] The content of LDH is greater in some tissues than in the myocardium.[1] Consequently, disease or operative trauma of organs other than the heart may cause a marked elevation of the serum LDH during the early postoperative period.

LDH is not a pure substance. In mammals it includes at least 5 distinct fractions. In 1957 Vesell and Bearn[6] separated serum LDH activity into 3 fractions or isozymes by electrophoresis. Analysis of the serum LDH of 2 patients who had sustained a myocardial infarction revealed that there was a selective elevation of the LDH fraction which migrated with the

α-1 globulins. They theorized that the 3 different LDH fractions (isozymes) originated in different tissues and suggested that the α-1 fraction was specific for myocardium. In 1958 Hill[7] separated serum LDH activity into 4 fractions or isozymes. In 1960 Wroblewski and associates separated serum LDH into 5 distinct fractions by electrophoresis. They also separated and quantitated the LDH activities obtained from homogenates of various organs and tissues. They found that the myocardial LDH activity was generally in the fourth and fifth LDH fractions (LDH_4 and LDH_5, according to their nomenclature). They also analyzed the serum LDH of patients who had sustained a myocardial infarction and found that there was a selective rise of the LDH and LDH isozymes.

In 1958 Hill noted that the different LDH isozymes exhibited different heat stabilities. In 1961 Strandjord and Clayson[4] demonstrated that LDH of myocardial origin was much more heat stable than LDH of hepatic origin. They measured the serum values of LDH and LDH in normal patients, postoperative patients, patients with congestive heart failure, patients with hepatitis, and patients with myocardial infarction and found that there was a rise of the LDH only in patients who had sustained a myocardial infarction. In 1964 Nachlas et al. reported studies of LDH and LDH in the presence of experimental myocardial infarcts. They found that the peak postinfarction serum values of the LDH" could be related more closely to the presence of a myocardial infarction than could the peak postinfarction serum values of LDH. The measurement of LDH in the present study is modified only slightly from the methods described by Strandjord and Clayson and by Nachlas, and associates.[18]

It seems that elevation of LDH to abnormal level during the postoperative period is a more specific indicator of the presence of a myocardial infarct than is a comparable elevation of GOT or LDH (Table II). The validity of the statement that an elevation of the LDH" beyond the normal range indicates the presence of a myocardial infarction and a lack of elevation of LDH beyond the normal range indicates the absence of myocardial infarction is 90 per cent, whereas, it is only 78 per cent for GOT and 68 per cent for LDH.

However, if one considers only the extreme elevations of GOT it too becomes a very valid indicator of the presence of a myocardial infarction. A rise of the serum GOT to a value greater than 65 units per 100 c.c. of serum (6 SD above the mean of normal values) has a diagnostic validity of 92 per cent. Extreme GOT elevations have been observed after operations upon the biliary tree in the absence of myocardial infarction.[8] Therefore, extreme elevation of serum GOT in the postoperative period after surgery of the biliary tract would be of unknown significance.

Summary

Elevation of the heat-stable lactic dehydrogenase (LDH) to abnormally elevated values seems to be a more valid indicator of the occurrence of a myocardial infarction intraoperatively or during the early postoperative period than are comparable elevations of GOT and LDH. However, if operations on the biliary tree are excluded, it seems that an extreme postoperative elevation of the serum GOT is also a valid indicator of the occurrence of a myocardial infarct. Since these conclusions are based upon data obtained from canine preparations, any clinical extrapolations that are made must be tentative.

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The combined influence of inhomogeneities and dipole location

Bipolar ECG leads in the frontal plane

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Contemporary progress in electrocardiography has been limited by the degree of accuracy with which the analytic model describes the cardiac generator and body-surface leads. In view of the electrical and geometrical complexities of the human heart and torso, simplified models have been employed and have proven clinically useful, as demonstrated by the use of Einthoven's model and equilateral triangle in electrocardiography.

Significant progress during the past decade has emanated from the Lead Vector and Image Space concepts introduced by Burger and Van Milaan, which were extensively utilized by Frank. Schmitt's application of transfer impedance and the Lead Field method of McFee and Johnston. These various ideas, mathematically similar in their end result, permitted freedom from several of Einthoven's simplifications. In particular, their derivation does *not* assume that the human torso is conductively homogeneous, of large extent, or possesses any particular boundary configuration. Also, in theory, the equivalent dipole generator may be located anywhere within this heterogeneous, irregular torso. However, laboratory studies and practical applications have generally considered locations of the dipole within the left-central thorax, and hence not too eccentric.

The essence of the Lead Vector and Lead Field theories is that the electrical properties of a particular lead can be quantitatively described by a vector quantity, the *Lead Vector*, and at each instant during the cardiac cycle the lead's voltage is equal to the scalar (dot, inner) product of the variable heart-dipole vector and the Lead Vector, the latter being stationary or time invariant. Thus the variation of the lead voltage is generated by the time

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varying magnitude and direction of the heart-dipole vector alone.

The virtue of this model is the separability of parameters of the heart generator and the conductive medium, respectively, which influence the lead voltage. The conductive properties of the torso are accounted by the Lead Vector, which lumps the effects of inhomogeneities, boundary shape, the location of electrodes and their relation to the source of potential. The last of these indicates that the heart dipole's point of location within the torso is a parameter which in general influences a lead's vector. Contemporary electrocardiography treats the properties of a lead as constant during the cardiac cycle; hence the lead's vector is also constant. Thus an underlying assumption is revealed, namely, that the point of location of the equivalent heart dipole is fixed during the cardiac cycle.

Since depolarization does progress through the myocardium, the real source of potential is not fixed in location except that it is confined to the cardiac region. The variations of lead vectors accompanying changes in location of the heart dipole have received attention, particularly with regard to the design of vectorcardiographic leads.[11] However, most quantitative observations have been limited to homogeneous models of the torso. The principal objective of the present study was to compare the variations in lead vectors on a homogeneous torso to those on a heterogeneous torso produced by identical changes in location of the heart dipole. Sufficient data was obtained to provide the entire map of each torso's boundary in image space, from which any lead vector of interest may be derived. Also, our experimental framework permits the separate quantitative effects of inhomogeneities and dipole location to be observed.

Specifically, we first observed the variation in lead vectors produced by precise changes in location of a dipole within the cardiac region of a homogeneous torso model. The observations were then repeated for identical changes in the dipole's location within two heterogeneous torso models, one with lungs and another with lungs and intracardiac blood. Thus, it was possible to observe that the variations in lead vectors and the torso's map in Image Space produced by changes in the dipole's location were much greater in the heterogeneous than in the homogeneous torso. In terms of Lead Field theory, the equivalent statement is that a lead's field, and hence performance, was considerably more nonuniform through the cardiac area of a heterogeneous torso than a conductively homogeneous torso.

Also, a particular lead of interest was examined, namely, the neck-to-left leg lead which provides the vertical lead in McFee and Parungao's[12] orthogonal VCG system and Frank's[13] precordial VCG system. This lead proved to be an excellent vertical lead in the homogeneous model, as previously described by others, but deteriorated badly in the heterogeneous model where its performance was highly nonuniform.

Methods

The technical ease of constructing accurately scaled models of the torso from electrically conductive paper prompted our use of this material in the present investigation. Varied and precise degrees of inhomogeneities are not easily introduced into three-dimensional models of the torso. However, qualitative and often quantitative inferences can be drawn from observations on two-dimensional (2 D) models.[11,14]

A 2 D celluloid template of a human torso's frontal plane was constructed to scale with overlying grid lines (Fig. 1). The lungs and heart were drawn upon it and the boundary points numbered. All models were constructed from this template, thus insuring that the torso shape with numbered boundary points, the outline of the lungs, and the outline of the myocardium were constant for all models. Also, the grid permitted myocardial dipoles to be located at exactly the same points, respectively, on all models.

Torso forms were cut from conductive paper (Teledeltos) using the template. For the homogeneous conductive model no further treatment was required. A second model simulated the increased resistivity of lung tissue. Throughout the model's lung region a grid of holes was punched. The ratio of hole diameter d to hole spacing s (ratio d/s) determines

the relative increase in resistivity of the punched area. The second model had the lung's resistivity increased by a factor of four thus corresponding to the best value of tissue resistivities determined from the literature.

A third model had the lung resistivity increased by a factor of four as described above but also simulated the heart's blood by *decreasing* the resistivity of the ventricular chambers area to one half This is done by painting silver disks (opposite effect from punching holes) and again the ratio of disk diameter to center spacing determines the relative decrease in resistivity (increase in conductivity)

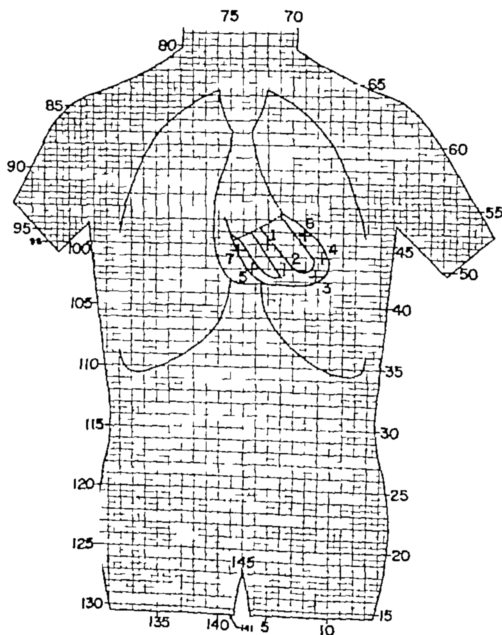


Fig. 1 Template for models of the torso frontal plane.

The values for I corresponding to particular alteration in resistivity of a 2-D conducting medium have been previously determined. A fourfold increase in resistivity is accomplished by punching holes such that d s = 0.86. The conductivity is doubled by painting conductive disks such that d s = 0.80. We verified these values of d s by measuring the resistivity of square pieces of paper before and after punching holes and painting disks.

After the paper models were constructed they were each stapled to a plywood board with overlying metric grid. The staples were carefully placed so that they entered the Teledeltos paper at each numbered point around the boundary. Electrical contact between staple and paper was assured by placing a small drop of silver paint on the point where the staple pierced the paper. Thus, each staple served as an electrode for measurement of voltage at the boundary point.

Within the region occupied by the heart's ventricular muscle, seven dipoles were located. Each dipole consisted of a pair of points with 1 cm. separation oriented horizontally (X axis direction) and a similar pair oriented vertically (Y axis direction). These four points were marked and electrically permanized with a tiny drop of silver paint on the paper. The four silvered points—X pair and Y pair—were symmetrically arranged around a central point, considered to be the dipole's location. The template with grid was used to position each dipole on each model, thus assuring that a particular diploe had exactly the same location on each model. The locations of the seven dipoles (Fig. 1) were the high and low regions of the septum, the ventricular apex, and the right and left ventricular free walls.

A dipole was energized by passing a constant unit current first through the horizontal pair of silvered points, thus providing a unit current dipole in the X axis direction, and the voltage at points around the boundary was measured with respect to point no. 141 on the right leg. The procedure was then repeated while the dipole's vertical pair of silvered points was energized to provide a dipole in the direction of the Y-axis. These two groups of measurements provide the X-components and Y-components, respectively, of the lead vectors for the simple bipolar leads, each lead consisting of a particular boundary point and the reference point on the right leg. The constant unit current energizing a dipole was continuously monitored with a sensitive ammeter.

Each of the seven dipoles was energized in each of three models yielding 21 sets of data, which were punched on cards for use by machine and computer.

Image space curves. The boundary's representation in Image-Space was obtained by employing the card punched data as input to an X-Y plotter which graphed these points, and then connecting successive points on each graph with straight lines to form a closed curve. Twenty-one image space curves were so constructed, each curve corresponding to a particular dipole location in a particular model.

Since boundary point no. 141 was selected as the common reference point, its corresponding point on the Image-Space curve lies at the origin (point 0,0). Had a different boundary point been chosen for reference, the Image-Space curve would undergo a translation (but not rotation) in the plane, since the reference point must map onto the origin. Also, the shape and size of the Image-Space curve is unaffected by the choice of reference point. From the Image-Space curve, the lead vector for any bipolar lead is readily obtained by drawing a straight line between the two points on the Image-Space curve corresponding to the two boundary points comprising the bipolar lead. This straight line is the lead's vector, and immediately makes evident the lead vector's magnitude and orientation.

Results

Fig. 2 consists of 21 Image-Space curves—seven dipole locations in each of the three models described above. Around each closed curve every tenth point is numbered to indicate the corresponding boundary point of the model, every fifth point is indicated by a protruding line, the midline point at the neck, point no. 74, is marked by a heavy dot, the midline

A portion of these results has been presented.[17]

point between the legs is point no. 145. Inscribed within each Image-Space plot is the Einthoven (Burger) triangle employing point no. 96 on the right arm, point no. 50 on the left arm and point no. 10 on the left leg.

Certain results are immediately evident from examination of the Image-Space plots and the lead vectors for standard leads I, II and III. In Fig. 2 looking down a column makes evident the effects of inhomogeneities within the volume conductor. Each column corresponds to a particular dipole location: the homogeneous model is at the top, next below is the model containing lungs of resistivity four times the general model, at the bottom is the model containing lungs and heart's blood. It is evident that inhomogeneities alone produce major effects on lead vectors, related surface potentials, and the torso's representation in Image-Space. The quantitative effect upon any surface lead of interest may be derived directly from Fig. 2.

The most important result of our model experiments is that the dependence of lead vectors and Image Space curves upon the dipole's location is often considerably greater in the heterogeneous models than in the homogeneous model. This can be visualized, for example, by comparing the amount of variation in the Einthoven (Burger) triangle as the dipole successively assumes locations no. 1, 5, and 7 in the homogeneous and heterogeneous models, respectively. The effect of dipole location within each model is seen by looking across each row of Fig. 2: the homogeneous model is the top row, the model with lungs is the second row, and the model with lungs and heart blood is the bottom row. Dipoles no. 5 and no. 7 in the right ventricular free wall may be considered centric, lying near the torso's midline on either side (see Fig. 1). Dipole no. 1 in the upper septum is mildly eccentric. For each of these dipole locations, the boundary of the *homogeneous* torso mapped into a circle and the Burger triangles varied slightly from equilaterality. In contrast, changing the dipole's location between points no. 1, 5, and 7 in either *heterogeneous* torso model produced marked variations in the Image-Space curves and Burger triangles. Also, further variations accompanied movement of the dipole to location no. 2 in the lower septum, no. 3 at the apex, and no. 4 and no. 6 in the left ventricular free wall.

Discussion

Method of the lead vector. The original Einthoven postulates include the assumption that the torso is a linear conducting medium. This permits a dipole generator to be vectorially represented and the operations of linear algebra (e.g., projection, representation by axial components, scalar product) to be employed. Consequently, a dipole vector may be decomposed into its orthogonal components, the respective contribution of each component to the lead voltage determined, and the respective contributions summed to yield the total lead voltage produced by the original dipole. This is the approach of the lead vector. Numerically, the X component of a lead vector (L_x) is the voltage produced in the lead by a unit dipole in the direction of the X-axis. Then the voltage contribution (V_x) of the heart vector's X-component (H_x) is simply that component multiplied by the lead vector's X-component, i.e., $V_x = H_x L_x$. Identical treatment of the Y and Z components provides the expression for the total voltage in a lead whose lead vector is $\bar{L}(L_x, L_Y, L_z)$ resulting from the heart vector $\bar{H}(H_x, H_Y, H_z)$ as follows:

$$V = V_x + V_Y + V_z$$
$$= H_x L_x + H_Y L_Y + H_z L_z$$

The experimental approach employed in our study was that of the lead vector. A unit current dipole was energized in the horizontal and vertical directions, in turn, and respective boundary voltages measured. This provides L_x and L_Y for bipolar surface leads, each lead consisting of a general boundary electrode and the reference electrode on the right leg. The set of lead vectors for a particular dipole location is plotted and the resulting figure is the boundary's representation in a vector space referred to as *Image Space*. From this graph in Image Space the lead vector for any surface lead, whether a simple bipolar lead or a complicated lead with multiple electrodes, can be determined

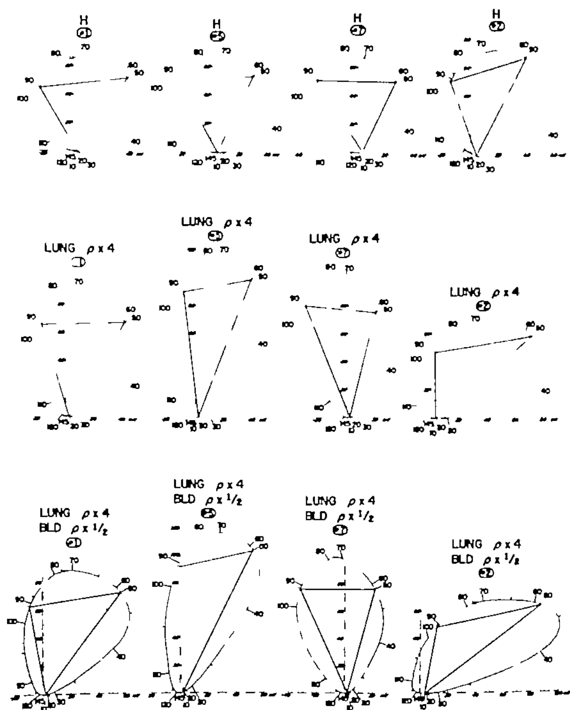


Fig. 2. Image-space curves with inscribed Einthoven (Burger) triangle for seven different dipole locations (the vertical columns) in each of three conductive models (horizontal row). Top row: the homogeneous model H. Middle row: heterogeneous model with lung resistivity increased fourfold ρ × 4. Bottom row: heterogeneous model with lung resistivity increased fourfold and the intraventricular blood resistivity decreased to one half.

by vector addition (subtraction) preceded by suitable weighting where indicated

Method of the lead field In the execution of a lead field experiment a unit current is impressed upon the surface lead so that current flow through the volume conductor is from the positive to negative electrode or terminals of the lead While current flows a voltmeter determines the direction of maximum voltage increase at the cardiac point of interest and the magnitude of the voltage increase per unit distance. This vector is called the gradient vector and the current flows down the gradient (opposite direction) The gradient

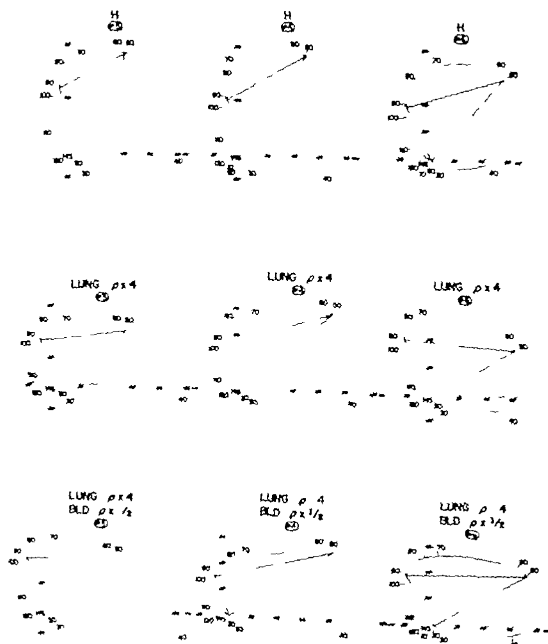


Fig. —Cont d The dipole locations appear in Fig. 1

vector at this point is identical to the lead's vector for a dipole located at this point of measurement

In contrast to the method of the Lead Vector the graphical result of a Lead Field experiment is a plot of the current flow lines, or streamlines within the cardiac region resulting from the flow of a unit current through a surface lead This describes the performance of only one lead but for all possible locations of the heart dipole For each independent lead of interest another experiment must be performed This is one reason that we have preferred the Lead Vector method when the totality of boundary leads is of interest for only several representative dipole locations

Inhomogeneities Regardless of whether the Lead Vector or Lead Field method is employed assessment of the relative importance of conductive inhomogeneities requires parallel experiments with volume conductors both with and without the inhomogeneity being considered It seemed probable to us that the most important of the torso's inhomogeneities was the lungs, in view of their large extent and proximity to the heart Our model experiments did indeed demonstrate substantial differences in lead vectors between the homogeneous medium and that possessing lungs. The discrepancy was most marked for dipole locations in the cardiac apex and the ventricular free walls. This probably is due in large part to the proximity of these locations to the refractive interface between the myocardium and lung two regions of very different conductivity The smallest discrepancy was for dipole no. 1 located in the upper ventricular septum but even for this location the changes in lead vectors produced by introducing the lungs were quantitatively important.

Compared to the model possessing lungs, the addition of the heart's blood produced further changes in lead vectors and Image-Space curves but these were less striking than those accompanying the introduction of lungs. Nevertheless, these changes were of quantitative importance for some lead vectors the change being as much as 25 per cent in magnitude and 30 degrees in angle

The foregoing indicates the importance of modeling at least the lungs and heart's blood in volume conductors used to provide quantitative data applicable to man This conclusion bears directly on contemporary VCG systems. Fig 2 demonstrates that the performance of VCG systems employing simple bipolar leads (e g Cube and Tetrahedron) is highly dependent upon the presence of inhomogeneities. The more popular corrected systems (Frank precordial Schmitt SVEC III McFee axial) are similarly affected though a quantitative assessment requires calculation of the lead vectors for the axial leads of such systems. However the nature of the problem of correcting leads is indicated by the following remarks concerning Frank's precordial system [1]

The horizontal right-to-left lead (X axis) is basically provided by the electrodes designated *I* and *A* located respectively on the right lateral chest and left lateral chest in the midaxillary lines at the level of the ventricles. However this bipolar lead applied to a ***homogeneous*** torso had a lead vector which slanted backward about 13° The point to be appreciated from our data is that when applied to a ***heterogeneous*** torso the property of this lead is not known with any accuracy Nevertheless, Frank corrected for this 13° slant by suitable weighting of electrode *C* on the midprecordium again based upon the performance of electrode *C* in the homogeneous torso, and this was combined with electrode *A* The final lead's vector may be conveniently thought of as a weighted linear combination of two lead vectors one for the bipolar lead *A I* and the other for bipolar lead *C I* It is clear from our model experiments that the performance of the final lead in the human ***heterogeneous*** torso can not be specified from measurements on a homogeneous model and further probably varies considerably as excitation moves through the myocardium

Dipole location Application of the lead vector assumes that the heart dipole occupies a fixed location during depolarization and consequently the lead vector does not vary during this interval In reality the excitation process, with its attendant sources and sinks, does move

through the myocardium Therefore one objective of corrected leads is to synthesize a lead vector *which is invariant under* changes in dipole location within the cardiac volume. Such a lead has a uniform lead field within the cardiac volume i.e. electrically energizing the lead produces parallel flow lines and uniform current density within the region of the heart

The VCG system recommended by McFee and Parungao[12] employes a bipolar lead between the left side of the neck and the left leg to provide the Y axis (vertical longitudinal) lead Frank's[11] precordial system also uses electrodes on the neck and left leg to provide the vertical component but the lead vector for the neck to-leg lead on Frank's homogeneous torso model had a significant back to-front component This Z component was eliminated with the use of an electrode on the back which produces a negligible change in the lead vector's frontal (X Y) plane projection *in the homogeneous model* Frank specifically evaluated the effects of dipole location upon this lead's vector and found that dipole translation within a 5 cm cube resulted in variations of 20 per cent in length and ± 5° in angle.

The effect of dipole location on the performance of a neck leg lead was evaluated in our models. The lead vector for this pair of electrodes was drawn from the Image-Space curves in Fig 2 by connecting boundary points no 74 (neck) and no 10 (left leg) and then translating point no 74 to the origin of the frontal plane. The comparative performance of this lead in the homogeneous model and the model with lungs and heart's blood is illustrated in Fig 3 In our homogeneous model the neck-leg lead performed very well as a

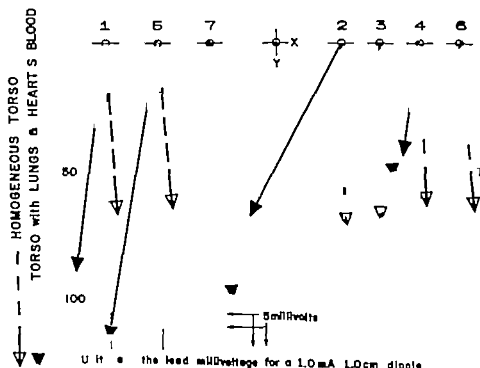


Fig 3 Lead Vectors for bipolar leg-to-neck lead, determined for seven dipole locations (nos 1 5 7 2 3 4 and 6) in both homogeneous torso (dashed vectors) and one with relatively lungs and conductive intra ventricular blood (solid vectors). The leg-to-neck lead is the basic connection employed to measure the Y-component of the heart vector in several contemporary VCG systems (Frank precordial and McFee orthogonal systems). In the homogeneous torso the leg-neck lead performs very well, always being nearly vertical and varying about 10 per cent in strength. In the heterogeneous torso the lead performance deteriorates badly varying over 35° in angle and nearly threefold in strength. This illustrates that major errors will result when lead performance in the nonhomogeneous torso is presumed from measurements on homogeneous model.

vertical axis, demonstrating a variation of about 4° in orientation and 10 per cent in magnitude as the heart dipole changed location among the points studied. In contrast, this lead's performance in the heterogeneous medium containing lungs and blood was not satisfactory, demonstrating a range of variation in angle of 35° and more than threefold range in magnitude. This clearly illustrates that inhomogeneities of the type existing in the human torso not only exert a major influence on lead vectors but accentuate the effects produced by changes in location of the heart dipole, making dipole location even more critical than in a homogeneous medium. Thus, a surface lead which possesses a uniform lead field through the heart region in a homogeneous medium will generally deteriorate considerably when applied to a heterogeneous torso whose inhomogeneities are disposed as are the lungs and blood of the human torso. The use of homogeneous models for the study and design of the currently popular orthogonal VCG systems probably accounts in part for the quantitative discrepancies between vectorcardiograms obtained with these various lead systems. It would appear that homogeneous models are unsatisfactory for the quantitative study and design of leads to be used in man. This conclusion applies not only to VCG leads, but also to higher order leads referred to multipolar models of the cardiac generator.

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A computer method for studying the postexercise ballistocardiogram*

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Artifactual problems inherent in cardiac monitoring are of major importance in cardiovascular research. The main difficulty is usually found in the area of a wandering baseline or in artifacts secondary to muscle tremor or vigorous respiration. These have been difficult problems to solve in electrocardiography, especially in records obtained during and after exercise. One means of solution has been the use of the Computer of Average Transients (CAT)*†[1,2] which has made it possible to retrieve readable records from those which appear illegible due to artifacts that were induced by movement and respiration.

These same problems have made the study of the ballistocardiogram (Bcg) difficult in the postexercise state. Since the Bcg is a mechanical method of measuring cardiac forces, body movement secondary to respiration and muscle tremors produce artifacts that appear more frequently and are thus more significant than those noted in the electrocardiogram (ECG).

It has been demonstrated that Bcg waves may be retrieved from records in which respiratory artifacts appear.[1,3] Since certain portions of the postexercise Bcg are shown to be important in the identification of healthy persons and those with coronary heart disease, it seems of interest to delve further and on a larger scale into the use of the postexercise Bcg. Because of common record distortions it became necessary to use a device such as the CAT for this purpose. An electronic system had to be devised for use with this computer in analyzing the Bcg records. Such a system and its use in preliminary basic studies are described here.

Methods

The subjects were 10 enlisted research volunteers who ranged in age from 18 to 20 years. They were accepted as subjects only after a thorough clinical examination, resting and postexercise ECG's, and a cardiac series of x-ray films had confirmed the lack of significant disease of any type.

The chief value of the CAT is in providing records from which artifacts have been removed by averaging so that randomly occurring record artifacts algebraically cancel each other. The resultant is not a true average since the computer

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actually add so that random positive and negative artifact added together will approximate (average) zero. Regularly recurring items reinforce themselves so that the resulting record is cleared up and interpretable. The differences between the system used in the present study and the one suggested by Rautaharju and Blackburn for use with the ECG are:

1 The same signal for analysis by the computer is not used as a trigger signal to start computer analysis; this eliminates the need of delay lines which tend to introduce amplitude errors. In our study the analyzed signal was the Bcg and the ECG signal was used as the trigger signal.

2 The Bcg was not filtered or smoothed out; the signal was fed into the computer just as it had been recorded.

3 The resultant curves were not normalized. A constant number of complexes were used in order to maintain consistency in amplitude comparison.

4 The R wave was not differentiated when triggering the computer in our initial study. The peak value of the R wave was used instead. A trial using a differentiating circuit (1.5 uf capacitor with a 10,000 ohms resistor) revealed that differentiation did not significantly change our resultant curves. However, under certain conditions its use was suggested (see Discussion).

Low frequency longitudinal acceleration Bcg's obtained during held midexpiration and normal respiration phases were recorded from an Astrospace airbearing bed as described in an earlier report[4] before and after standardized exercise which consisted of the double Master test or modified Harvard step test.[5]

A single exercise study consisted of one of the above tests with control, immediate, and 1, 2, 3, 4, and 5 minute postexercise recordings. Magnetic tape recordings* were made of the Bcg and ECG in each case. A voice channel was used for later localization of specific segments of the records. The Bcg and ECG were recorded on paper (modified Sanborn 964) for later comparison with the CAT readout, and an oscilloscope was used to monitor the input to the tape recorder.

The standard Lead II ECG signal obtained from the subject was used as a trigger signal to initiate computer analysis. This was necessary because of the pseudoperiodicity of the Bcg signal which would have made trigger relations to the analyzed complex erratic. Amplifiers 1 and 2 (Fig. 1) were used to raise the amplitude of the ECG signal to a suitable recording level. Amplifier 2 provided single-ended output to the input of the magnetic tape recorder. A Donner accelerometer[?] (longitudinal axis) mechanically attached to the Bcg bed provided the Bcg signal. The output of the accelerometer was then fed into amplifier 3 through a passive network used for filtering, attenuating, and calibrating (high cut-off frequency was 35 Hz). Amplifier 4 was used to provide single-ended output to the input of the tape recorder.

The pulse generating circuit controls the time at which the computer starts the analysis. The input circuit of this device consists of an attenuator and a diode (Fig. 2). The diode prevents transmission of any negative voltages. The attenuator or potentiometer is adjusted in such a way that the peak of the R wave is the firing voltage. Since the peaks of different R waves vary slightly with respiration, the attenuator was set so that the lowest in amplitude of the different R waves starts the analysis. Difference in the amplitudes of the different peaks of the R waves will result in different starting points in time for computer analysis. Addition of the differentiating circuit is illustrated in the Fig. 2 inset.

Before analysis was started, amplifier 5 (Fig. 3) was well balanced (zero output with zero input) because any imbalance in the positive direction will make the computer start prematurely; likewise any imbalance in a negative direction will delay the computer start. For the well stabilized amplifiers this was not a significant problem.

For analysis, the recorded Bcg signal was played back directly to the input of the CAT. The ECG was fed into amplifier 5 to raise the amplitude of the R wave to approximately 3 V, and the output of this amplifier was then routed to the square pulse-generating circuit that in turn started the computer analysis.

*Ampex FR 300

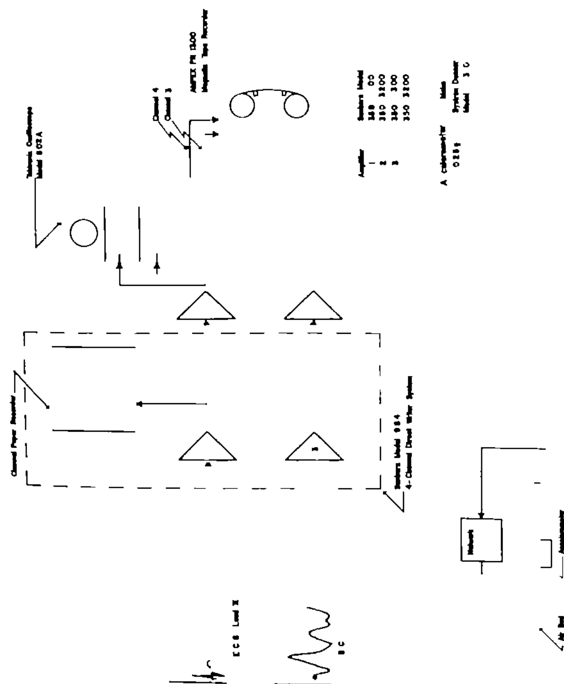


Fig 1 Block diagram of the instrumentation system nd recording method

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The cardiocirculatory changes caused by intravenous Dilantin and its solvent

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In 1956 an intravenous preparation of diphenylhydantoin (Dilantin) became available commercially. It is prepared by dissolving the drug in a solvent which contains 40 per cent propylene glycol, 10 per cent ethyl alcohol, and water, with the pH adjusted to 11. A high pH is required because Dilantin is poorly soluble in a less alkaline aqueous solution. It was introduced in this form with a suggested initial dose of 250 mg. or less for the management of status epilepticus. Since that time increasing doses have been used with a maximum starting dose as high as 1,000 mg.

Some of the side effects that were previously recorded with intravenous Dilantin are hypotension, disturbances of cardiac rhythm, prolongation of P-R intervals and QRS complexes, and alterations of the S-T segments and T waves in the electrocardiogram (ECG). Most of the reports of untoward cardiac reaction originated from experiments on animals,[1-4] although a number of patients have developed increasing degrees of heart block or even cardiac arrest after treatment with Dilantin.

In this setting, the introduction of parenteral Dilantin as a treatment for cardiac arrhythmias seemed paradoxical. However, careful evaluation of rhythm disturbances has indicated that it may be a safe and useful drug in the therapy of ventricular premature beats and ventricular tachycardia, particularly when these disturbances result from digitalis intoxication.[5-9] In our laboratory its efficacy has been related to the maintenance of a critical blood level.

In recent investigations into the effects of intravenous Dilantin in cats which were made epileptic with penicillin, we have observed certain untoward effects of intravenous Dilantin which appear to be related to the effects of its solvent on the heart rate, blood pressure, and ECG. This report contains an analysis of these phenomena.

Method

Twenty adult mongrel cats that weighed from 2 to 4 kilograms were anesthetized with 30 mg. per kilogram of pentobarbital intraperitoneally. Two of these animals were premedicated with atropine sulfate

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(0.009 to 0.026 mg per kilogram) and another two were subjected to bilateral section of the vagi in the neck.

Blood pressure was measured in the femoral artery with a Statham SP-4 pressure transducer. Respiration was recorded with a silicon mercury strain gage which encircled the thorax via a Parks Model 270 plethysmograph. Four ECG leads were recorded: I, right forepaw to left forepaw; II, right forepaw to left hindpaw; III, left forepaw to left hindpaw, and one precordial lead. All recordings were led into an ink-writing Grass Model 5 polygraph.

The effects of the following intravenous solutions were investigated: (1) propylene glycol 40 per cent in water (at pH 6 and also adjusted to pH 11 with sodium hydroxide) (0.5 to 2.5 ml. per kilogram); (2) the Dilantin solvent (prepared by Parke Davis, pH 11) (0.5 to 2.5 ml. per kilogram); (3) N/100 sodium hydroxide (pH 11) (0.5 to 2.5 ml. per kilogram); (4) 10 per cent ethyl alcohol solution (0.5 to 2.5 ml. per kilogram); (5) Dilantin in N/100 sodium hydroxide (25 to 50 mg. per milliliter); and (6) Dilantin in 40 per cent propylene glycol or in the Parke Davis Dilantin solvent (25 to 50 mg. per milliliter).

Injections were made at various rates through a catheter placed in the femoral vein. Rapid injections were made manually; slow injections of 1 ml. per minute or less were made with a Model 600-930 VDC Harvard infusion pump.

Results

The effects upon the cardiorespiratory systems of the solvents alone and the preparations containing Dilantin will be presented separately. These effects were constant and reproducible in all the animals.

The effect of solvents. The 40 per cent propylene glycol alone and the solvent supplied by the manufacturer had identical cardiac effects, and the majority of these were counteracted by Dilantin.

A dose of 0.5 to 1 ml. per kilogram which is 1½ to 3 times the dose used in man was injected rapidly (1 to 5 seconds) in the first experiments. The smaller dose produced the following changes: A rapid transient reduction of blood pressure of as much as 20 mm. Hg systolic and 30 to 40 diastolic occurred and lasted for ½ to 4 minutes; a brief period of apnea lasted 10 to 15 seconds (Fig. 1,A). Bradycardia (Fig. 2,A) occurred, as did a sudden transient alteration in the electrical axis of the heart which outlasted the apnea and the reduction of blood pressure. There was also a marked augmentation of the amplitude of Q, R, and S waves in all leads which amounted occasionally to a doubling of all potentials (Figs. 1,A, 2, and 3). There was a marked amplification of T waves with an occasional reversal of their direction (Fig. 4,A, insets 2 and 3); this was persistent and lasted up to 15 minutes. Transient elevation of S-T segments occurred for a few seconds and was generally related to the period of maximum hypotension.

When the larger dose (1 ml. per kilogram) was injected rapidly, depression of the sinoatrial rhythm, with a release of nodal or multifocal ectopic ventricular rhythms, occurred (Fig. 5). Still larger doses (1.5 to 2.5 ml. per kilogram) produced temporary asystole (Fig. 4,B).

Rapid infusion of propylene glycol (1 ml. per kilogram) into the animals which were previously atropinized or vagotomized no longer provoked bradycardia, depression of atrial conduction, or ar rhythmia; the amplitude of the QRS complexes increased, and the blood pressure decreased (Fig. 2).

With slow infusions (1 ml. per minute or less) as much as 3.5 ml. per kilogram could be given with only minimal depression of blood pressure and respiration. Alterations of the T wave and S-T segment of the type described above occurred in all the animals and augmentation of ECG complexes occurred in most. Long runs of irregular premature ventricular beats occurred in a few animals.

Rapid or slow injections of N/100 sodium hydroxide in volumes of 0.5 to 3.0 ml. per kilogram did not significantly alter blood pressure, ECG, or respiration. Similarly, 10 per cent ethyl alcohol alone had no significant effects upon these functions.

When the animal was premedicated with Dilantin (10 to 25 mg. per kilogram) none of the changes otherwise produced by the

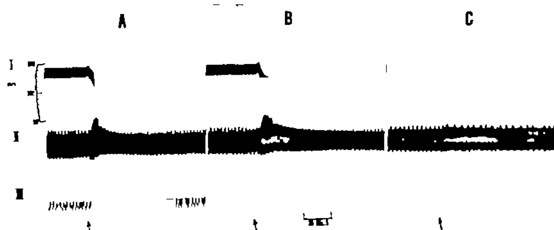


Fig. 1. Tracings at slow paper speed to show over-all changes in blood pressure and QRS amplitude in the ECG after rapid infusions of Dilantin, its solvent, or both. A cat weighing 2 kilograms was anesthetized with pentobarbital. *I*, blood pressure; *II*, standard Lead I of ECG; *III*, respiration. *A*, 2 ml of Dilantin solvent infused rapidly and intravenously caused moderate hypotension, marked augmentation of the amplitude of ECG complexes, and brief apnea. *B*, 25 mg of Dilantin in 2 ml of solvent caused marked hypotension and augmentation of ECG complexes. *C*, 25 mg of Dilantin in 2 ml of N/100 sodium hydroxide resulted in modest hypotension and no alteration of ECG amplitude. *Arrows* indicate the time of infusion. (The slight elevation of blood pressure immediately following the rapid infusion of 2 ml of fluid in each tracing is a hemodynamic response to the sudden increase of blood volume and is nonspecific.)

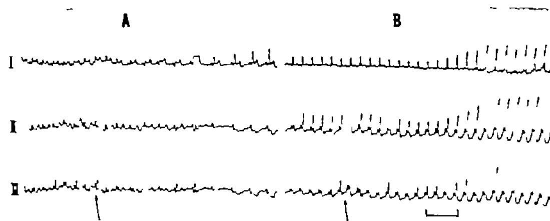


Fig. 2. A cat weighing 2.8 kilograms was anesthetized with pentobarbital. *I*, *II*, and *III* represent the standard ECG leads. *Arrows* indicate intravenous (1.3 ml/kg) infusion of propylene glycol. *A* was taken before section of the vagi; note slowing of rate after infusion. *B* was taken after section of both vagi; no slowing of rate occurred after infusion. Augmentation of the amplitude of the QRS complexes is visible in both tracings. Time marker (lower right-hand corner) indicates one second.

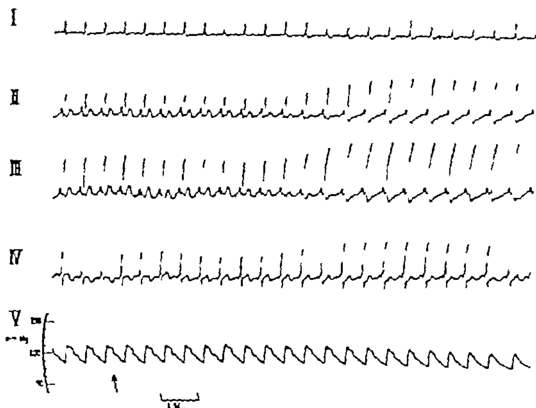


Fig. 3. A ... weighing ... kilograms anesthetized with pentobarbital and premedicated with 40 mg. of Dilantin. I, II, and III represent standard ECG leads. IV is precordial lead. V is blood pressure. The arrow marks the rapid intravenous infusion of ... ml. of Dilantin solvent which results in marked augmentation of R waves in II ECG lead.

rapid infusion of 0.5 to 1 ml. of propylene glycol could be evoked except the hypotension, some alteration of ST-T wave vectors, and the augmentation of the QRS complex. This augmentation was not affected in extent or duration by the premedication and it occurred without significant shift of the electrical axis of the heart (Fig. 3).

The continuous arrhythmias which were produced by the slow propylene glycol infusion were eradicated by subsequent intravenous administration of Dilantin in sodium hydroxide.

Dilantin in N/100 NaOH. Intravenous doses of 10 to 25 mg. per kilogram produced transient hypotension with reduction in a blood pressure of as much as 70 mm. Hg systolic and 25 mm. Hg diastolic that lasted 1 to 5 minutes (Fig. 1,C).

The heart rate slowed slightly but there was no change in the ECG.

Dilantin in propylene glycol. Infusion of Dilantin (dissolved in 40 per cent propylene glycol or in the Parke Davis solvent) rapidly produced hypotension of greater degree (a drop of 40 to 50 mm. Hg systolic and 50 to 60 mm. Hg diastolic) and duration (? to 10 minutes) than either constituent given alone (Fig. 1,B).

T wave and S-T segment changes of the type observed after the injections of propylene glycol were noted but these changes were very brief and were completely reversed within seconds (Fig. 4,A, inset 3).

The amplitude of Q, R, and S waves increased in precisely the same degree and for the same duration as when propylene glycol was given alone (Fig. 1,B).

Induced hypotension. A reduction of blood pressure approximately equal to that produced by propylene glycol was achieved by bleeding some animals and by infusing the sympathetic blocking agent, trimethaphan (Arfonad) into others.

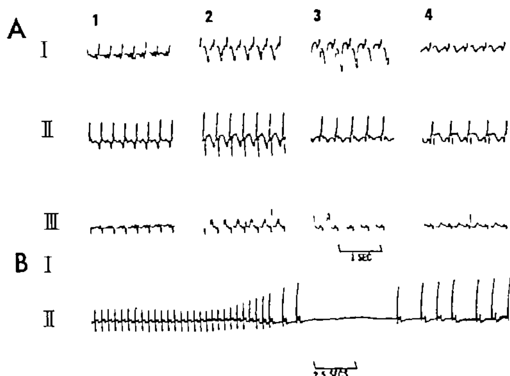


Fig. 4. *A*, A cat weighing 2.7 kilograms was anesthetized with pentobarbital. *I*, *II*, and *III* represent the standard ECG leads. In inset *1* the resting ECG is demonstrated. Inset *2* is immediately after the infusion of 2 ml. of Dilantin solvent and shows the amplification of R and S waves, S-T segment alteration, and deeply inverted T waves. Inset *3* follows the rapid infusion of 25 mg. of Dilantin in solvent and shows the deeply inverted T waves and the elevation of S-T segments which rapidly reverts to normal. Inset *4* demonstrates the effect of rapid infusion of 2 ml. of Dilantin solvent after premedication with Dilantin. It is evident that the deep T wave inversion shown in *2* and *3* is no longer produced, although some alteration of the S-T segments may be seen. *B*, A cat weighing 2 kilograms was anesthetized with pentobarbital. The shaded area in *I* represents the infusion of 5 ml. of Dilantin solvent. *II* is an ECG lead. Some amplification of R waves followed by brief cardiac arrest is evident in the ECG.

None of the ECG alterations that were caused by propylene glycol could be reproduced by these maneuvers.

Conclusions

There appear to be 2 mechanisms responsible for the abnormalities induced by a propylene glycol infusion. The prophylactic effects of atropine or vagotomy which prevent bradycardia, the depression of atrial conduction, and nodal rhythms induced by propylene glycol suggest that these phenomena are vagal reflexes. The amplification of the QRS complex seems to be most easily explained as a direct myocardial effect because it is neither reproduced by artificially reducing blood pressure nor abolished by atropine or vagotomy. Further studies on the mechanisms of these phenomena are now in process in our laboratories.

The practical significance of these observations is, however, important. In cats, propylene glycol produces definite disturbances of T waves, S-T segments, cardiac rhythm, and blood pressure. These deleterious effects are partially prevented by the Dilantin and, therefore, the concentration of solute (Dilantin) to solvent (propylene glycol) becomes crucial. The optimal concentration of solute to solvent in the treatment of cardiac rhythm disturbances has not yet been determined, but excessive dilution in the propylene glycol solvent is known to be hazardous.

The rate of administration of com

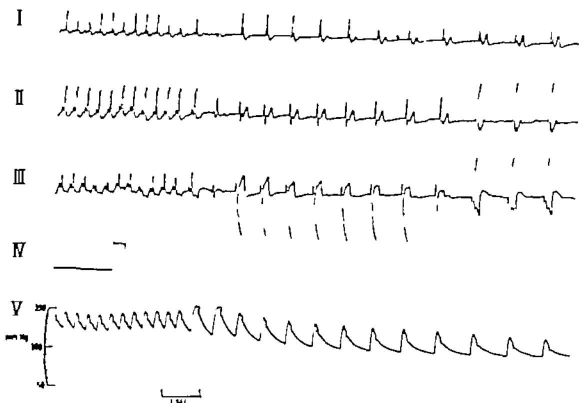


Fig 5 A t weighing 2 0 kilograms nesthetized with pentobarbital. I II and III represent standard ECG leads. The elev ted portion of IV indic tes the time of infusion of ml. of Dilantl solvent, and V is blood pressure After infusion an longation of the P P I terv l, followed by disappear nce of P es and the ppear nce of an ectopic foci becomes evident

mercially available Dilantin has also been shown to affect the cardiac consequences. Very slow administration can be accomplished without undue hypotension and with only moderate ECG changes. Rapid infusion results in severe hypotension (due to the additive effects of Dilantin and propylene glycol) and marked ECC alterations.

When Dilantin is given in propylene glycol and is combined in the usual con centration that are suggested by the manu facturer the latter appears to exert its effects upon the heart slightly before the Dilantin becomes effective. This fact too emphasized the need for slow administration particularly of the first few milli liters.

These studies, carried out on cats, may help to explain the reasons for some of the untoward effects that were previously en countered in animals which were given intravenous Dilantin. These studies sug gest the need for a reappraisal and standardization of the techniques of adn inistration of intravenous Dilantin in man

Summary

Disturbances of cardiac rhythm blood pressure and alterations of the ECG are produced by propylene glycol the solvent for parenteral Dilantin. Many of these phenomena are prevented by the Dilantin itself The proportion of Dilantin to sol vent the rate at which each acts upon the heart and the rate of administration may determine the consequences in any par ticular patient

A unique change in the forms of the ECC namely augmentation of all amplitudes, is produced by propylene glycol This phenomenon has not yet been ex plained

The authors are indebted to Dr Lawrence Scherr for guidance and criticism in preparing the manu script.

pentobarbital intubated (except for the turtles) and placed on artificial respiration. The chest was opened via the sternum. The breast plate was removed from the turtles. Recording electrodes were placed across the heart (electrodes *B* in Fig 1) A recording was taken with one electrode at the apex and the other cephalad to the aorta, and also a conventional lead II electrocardiogram was recorded. Stimulating electrodes 1 cm square were placed on each ventricle Calculation of current available from commercial stimulators indicated that the best of these provided sufficient current to stimulate a frog heart instantaneously but not a cat or dog heart. Consequently a condenser discharge stimulator was constructed (Fig 1) The capacitor used was 23 microfarads. The discharge through the heart was thus 0 1 joule for the high voltage (90 v) and 0 0001 joule with the lower voltage (3 v) These voltages were selected because preliminary trials indicated that the higher voltage would stimulate the entire heart and the lower voltage would not

To avoid large shock artifact a technique was used similar to one reported by van Dam and Durrer in which relays were used to short-circuit the recording leads during stimulation The stimulating circuit which was open during recording was closed by a relay in the stimulating lines. As seen in Fig 1 the relays were closed by pulses so timed that the shorting relays were activated for 15 msec beginning $3\frac{1}{2}$ msec before closure of the stimulating relay The stimulating relay was closed for 7 msec

The heart was stimulated during the minimum refractory period (preferably just after the P wave or at the beginning of the QRS) The ECG was monitored and recorded on a Rycom oscilloscope. When the heart was stimulated with a 3 v pulse duration of the resultant QRS complex increased while 90 v stimulus usually decreased its duration.

Results

Effect of shortening and lengthening QRS The average normal QRS duration was determined for each experiment and compared with the duration of the stimulus-produced QRS complex for that particular experiment only Thus, duration of QRS after stimulation could be evaluated both absolutely and in relation to normal QRS duration in that animal.

In 28 recordings (in both dog and cat) after stimulation QRS duration was shorter than normal. In 26 of these recordings, the T wave was unchanged as shown by the example in Fig 2 The T wave which ap-

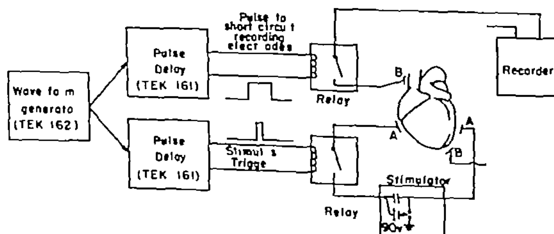


Fig 1 Apparatus used to stimulate the ventricle Rate of stimulation is set by the waveform generator (TEK 162). The upper pulse delay unit (TEK 161) short-circuits the recording system while the stimulus is being delivered. The lower waveform generator triggers the stimulus. The stimulator consists of battery and capacitor. Stimulating electrodes are labeled A recording electrodes B

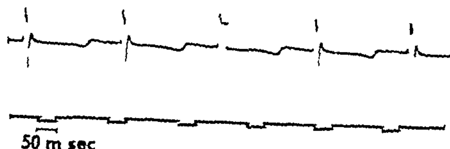


Fig 2 Two normal beats are followed by a supramaximal stimulus (dog). The QRS duration is shorter than normal but cannot be determined exactly because of the stimulus artifact. The T wave following stimulus is identical to control

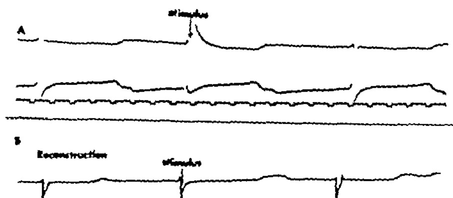


Fig 3 A normal beat followed by a stimulus in a turtle heart. In line A QRS is shortened in duration as can be seen from the lower record and the following T wave is lower than normal to QRS and identical to that of normal beat. Line B is reconstruction of altered T wave following QRS of increased duration

peared after a shortened QRS complex could be exactly superimposed over a T wave which had followed a normal QRS wave

Although many more recordings were obtained which had no change in the T wave following stimulation they are not included in the data above because shock artifact made it impossible to measure exactly the duration of the QRS complex.

In 90 recordings obtained following stimulation at low voltage the QRS complex was lengthened The resultant T waves displayed the same changes in polarity and shape as ordinarily seen in extrasystoles. Polarity changes were most common but approximately 30 per cent of the T waves showed only an increase in depth or height Five recordings showed no change in the T wave

Thirty-six recordings were obtained in which the QRS complex apparently was altered in shape but not duration In these the T wave was changed in 18 and unchanged in 18 The altered T waves were mainly characterized by a small increase in magnitude

The results obtained from turtles were similar to those from dogs and cats. Only one recording with a shortened QRS complex had a T wave with an altered wave form (inversion) When the QRS complex was shortened as in Fig 3,A the T wave was unchanged When the QRS complex was lengthened as in Fig 3 B the T wave was lengthened and more shallow Unlike the dog and cat the turtle did not show a change in polarity of the T wave.

Relationship of length of QRS to T wave change When the QRS was shortened by 2 msec or more (Fig 4) the T wave did not deviate from normal Conversely if the QRS was lengthened by 4 msec or more the T wave was always altered The

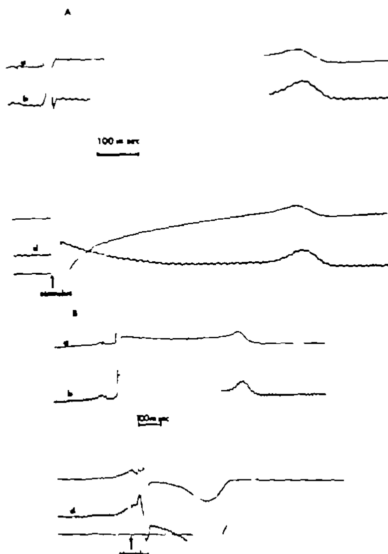


Fig 4 1 *A* normal beats are show t and *b* Shortened beat In and *d* show T wa identical to normal 1 *B* smaller stimulus amplitude produces lengthened QRS complex ith inverted T (and *d*, cat) Control record in od *b* shows longer ST segment than in and *d*

alternation n about 70 per cent of these T waves included a change n polarity The QRS complexes between 2 msec. shorter and 4 msec longer than normal were followed by some T wave changes, the number increasing as the QRS dura tion increased The change n T wave was minimal when the QRS duration was normal or 1 msec. below normal

The types of changes seen in the T wave were different at the various QRS dura tions (Fig 5) From a normal duration to 2 msec. below normal polarity did not change. In one case, depth of deflection was increased When QRS was of normal duration or up to 4 msec. longer than normal there were both increased depth of deflection and change in polarity the percentage of cases showing polarity change increasing as QRS duration increased

Discussion

It appears from these results that from to 10 msec. below the normal QRS dura tion (because of the measuring technique

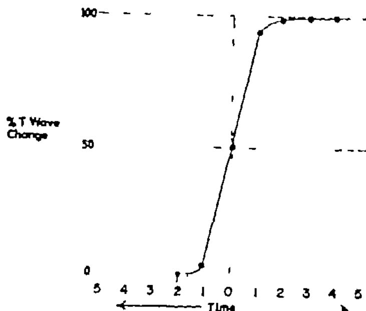


Fig. 5. Change of duration of QRS complex in milliseconds plotted against percentage of T waves showing changes in shape. Below normal duration (0) most T waves are unchanged. At normal QRS duration 50 per cent of T waves are changed. When QRS is lengthened larger percentage of abnormal T waves occurs. Points from which the curve was drawn are shown.

we had no *measurable* shortening greater than 10 msec. below normal and we have undoubtedly overestimated the duration of all QRS complexes shorter than normal) the direction of repolarization is not dependent on the pathway of depolarization, i.e., the pathway of depolarization can be altered markedly without changing that of repolarization.

The shape of the T wave appears to be more a function of the duration of ventricular depolarization than of the pathway of depolarization. Thus, within the QRS duration limits mentioned above, the sequence of repolarization may be more markedly influenced by external factors, such as myocardial temperature gradients, pressure gradients, and hypoxia[1,4,16] than by the sequence of ventricular depolarization. When the time interval required for all the cells to depolarize is sufficiently short, the above mentioned factors control the pathway of repolarization through the myocardium. However, when the QRS duration is lengthened, as in extrasystoles, the time interval between the depolarization of the earliest cells and the latest cells is long enough to override such factors as temperature (i.e., the cells first depolarized may even repolarize before the last cells are depolarized). These results also tend to confirm the point of view that the ventricular gradient has empirical and statistical significance rather than significance with respect to a cellular "linkage" between depolarization and repolarization.

It is possible that during stimulation at 90 v. we were changing the pathway of depolarization only slightly. This might happen if the Purkinje system is activated by the stimulus. Although the whole myocardium was apparently depolarized with a stimulus (as appeared from the records) it cannot be determined whether or not this depolarization was simultaneous for all parts. We can only say that the QRS duration following the stimulus was 15 msec. or shorter because the recording apparatus was disconnected by relays for 15 msec. Because of the size and placements of the electrodes, however, it seems highly unlikely to us that the pathway of depolarization would be only minimally changed with the massive stimulus. However, this possibility cannot be ruled out.

Summary

The pathway of depolarization of the ventricular myocardium was changed by a single pulse which stimulated the entire ventricular myocardium. The T wave following the stimulus was recorded and compared to T waves following a normal ventricular depolarization. It was found that when the QRS was not lengthened the T wave following the stimulus did not change. When the QRS was lengthened sufficiently the T wave following was always changed.

It was concluded that the normal sequence of repolarization is determined by factors other than the pathway of depolarization.

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Effect of chronic exercise on myocardial function

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The general recognition among investigators that cardiac hypertrophy follows severe and long-continued exercise. One of the most dramatic physiologic adaptations of the human body is that the heart may increase its mass of ventricular muscle in response to a chronic increased work load as with athletes or laborers who do heavy physical work. Yet curiously enough the increases in contractile strength and in size in hypertrophy are produced by mechanisms that are not entirely known. As a result of the common clinical finding of an increased mass as well as a dilatation in progressive chronic heart failure a great deal of emphasis has been placed on the functional significance of the adaptive mechanism of cardiac hypertrophy. In physiologic hypertrophy the increase in myocardial mass is predominantly the result of the enlargement of myocardial fibers rather than their multiplication. On the other hand when the work load is increased to a greater extent by a pathologic mechanism such as hypertension or aortic valvular disease which is not the case with the athlete or the laborer then the increase in myocardial mass is the result of multiplication of myocardial fibers as well as the increase in fiber size. Thus, the result is pathologic hypertrophy. Whether hypertrophy is detrimental because of an increase in the diffusion distance for oxygen and metabolites which produces ischemia has not been elucidated. That the hypertrophied heart is functionally superior to the normal heart remains a subject of considerable debate. Benzak,[1] Crimm and associates and Kerr and associates tend to support the theory that the hypertrophied heart is more powerful and is capable of producing greater tension than the normal heart. On the other hand evidence to support the theory that the hypertrophied heart may be functionally inferior is presented by Gregg and associates, Frank, Harrison and Wood, and Lauterbach.[7]

Forced swimming provides a convenient method for exposing small animals to exercise in a relatively controlled environment. Investigations of various physiologic and pharmacologic mechanisms have been conducted on animals that are forced to swim. It was the purpose of this study to observe the degree of cardiomegaly which is produced by swimming and to ascertain whether the intact hypertrophied heart is capable of developing more so-

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metric tension (potential work) than the intact normal heart

Methods

For the experiments 30 female albino rats of the Sprague Dawley strain (weight 214 to 264 Gm.) were divided randomly into 2 groups of 15 each a control group and an exercise (swimming) group. The animals were housed individually in an air-conditioned room and supplied with individual food cups and water bottles. They were fed ground Purina Laboratory Chow. Each animal's weight (twice weekly) water intake and daily food consumption were recorded

The animals swam in two metal tanks (30 by 22 inches) The depth of the water was about 14 inches, and its temperature was approximately 33° C In water near body temperature laboratory rats can swim for more than 50 hours—over 300 times longer than in water at 17° C and over 100 times longer than in water at 40° C. To acclimatize the rats to the novel environment they were made to swim for half an hour the first day and the time period was increased half an hour daily until 6 hours a day of swimming had been reached Subsequently the animals swam 6 hours a day 6 days a week, until 118 hours had been reached At this time the first animal was operated upon and the last animal was operated upon after a total swimming time of 250 hours. A control animal was studied at the same time as each exercised animal

All animals were anesthetized with pentobarbital, sodium 40 mg per kilogram intraperitoneally A tracheotomy was performed and artificial respiration was administered by a Phipps and Bird small animal rhythmic motor-driven respirator Polyethylene tubing (PE20 inside diameter 0.015 inches outside diameter 0.043 inches) was used to cannulate the left carotid artery (in order to record blood pressure) and the jugular vein (in order to administer drugs) A midline thoracotomy was performed and the heart was exposed for the measurement of isometric systolic tension (IST) with a strain gauge lever system [11] The 2 feet of the lever system were attached with silk sutures to an 8 mm. segment of the right ventricle. The right ventricle was used in all animals except for 2 control and 2 exercised animals. The left ventricle was used in these 4 animals to determine if there was any difference in the tension developed by the right and left ventricle The segment of muscle between the 2 feet was stretched to apply an initial tension of 5 10 20 30 and 40 Gm. above end-diastolic tension (EDT) The strength of myocardial contraction that developed under these specific and designated circumstances is an indication of potential myocardial contraction.[11,12] Blood pressure was measured with a Statham (P23Db) transducer heart rate was measured with a tachometer from impulses taken from the IST recordings. A Sanborn polyviso recorder model 154 was used to record all parameters After the completion of the IST recordings, the wet weight of the heart liver and adrenal glands was recorded The heart volume (calculated by immersion in saline) and the thickness of the left and right ventricular wall were recorded.

Results

As a method of providing exercise for rats the instigation of swimming is convenient but it is evident that more than muscular exercise is involved The stresses produced by swimming include the muscular movement produced by swimming the sympathetic reactions which may be accentuated by the psychologic stimulus of the life threatening environment and the increased heat loss through conduction to the water Observation of the behavior of the rats after swimming suggests that neural mechanisms may be disturbed by the rigor regimen of swimming. When removed from the water the rats appeared to be in a distressed condition and did not display normal behavior until after 5 to 10 minutes. They displayed varying degrees of chromodacryorrhea, a condition which was not blocked by 1 mg per kilogram of atropine A few animals had convulsions that lasted 3 to 5 minutes they required a much longer period for complete recovery than the animals that did not have convulsions. The ears, tails a[illegible] limbs of the e[illegible] rcised ani[illegible] were colder to th[illegible] [illegible]tan[illegible] he[illegible] trol anima[illegible] [illegible]

irritable and struggled to get free when removed from the water whereas the control animals remained docile

Fluid intake of the exercised rat was approximately 15 c c per day (29 per cent) more than that of the controls, and food intake was approximately 6 Gm per day (26 per cent) greater No attempt was made to control the weight of the animals, and there was no significant difference in weight between the 2 groups at the end of the experiment This may be attributed to the increased metabolism which accompanied the greater food intake in the exercised group

Fig 1 *A* demonstrates developed IST and Fig 1 *B* shows the IST response to 3 μg per kilogram of epinephrine The response to epinephrine was much greater in the control group

Table I shows the IST developed at 5 10 20 30 and 40 Gm above end-diastolic tension The difference in developed IST between the control group and the exercised group was not statistically significant at 5 Gm and 40 Gm however there was a significant difference at 10 Gm 20 Gm and 30 Gm There was no significant difference in blood pressure between the 2 groups Mean blood pressure was 127 mm Hg in the control group and 130 mm Hg in the exercised group Heart rate was 21 per cent lower in the exercised group

Cardiomegaly and hepatomegaly were produced by exercise Table II shows the mean weights of the bodies adrenal glands, hearts and livers of the control and exercised animals. The mean values for heart weight were 0 901 Gm (S.E 0 009) in the control animals and 1 206 Gm (S.E 0 030) in the exercised animals. The mean values for liver weight were 8 166 Gm (S.E 0 17) in the control animals and 10 997 (S.E. 0 30) in the exercised animals The differences between the mean heart weights and the mean liver weights for the 2 groups are statistically significant The probability of chance occurrence of the difference in heart weights is less than 0 1 and less than 0 005 for the liver weights. There was no significant difference in the weights of the adrenal glands of the 2 groups

Other recorded measurements included heart volume (33 per cent greater in the exercised group) and thickness of the right and left ventricular walls. The thickness of the wall was determined in all instances by cross section at the base of the anterior papillary muscle There was a 39 per cent increase in the thickness of the right ventricular wall and a 36 per cent increase in the left. This was not a significant difference between the left and right ventricles. That both increased in thickness is probably the reason why measurements of the contractile force were the same for both Therefore the 2 animals in each group in which contractility of the left ventricle was measured were included in Table I

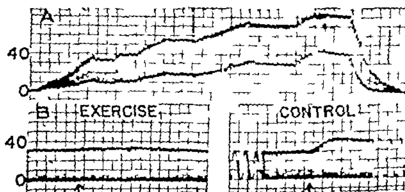


Fig. 1 Isometric systolic tension in grams (1 mm. on chart 2 Gm tension) Chart speed, 1 and 25 mm /sec. *A* Developed tension at various end-diastolic tensions. *B* A typical response to 3 μ/kg of epinephrine intravenously (arrow) in an exercised animal and control animal at end-diastolic tensions of 8 and 10 Gm. respectively

along with the 13 in each group in which the right ventricle was used Due to the position of the rat heart in the pleural cavity it is preferable to suture the lever system to the right ventricle rather than to the less accessible, left ventricle.

Discussion

The results show that the exercise of swimming produces a significant cardiac hypertrophy in albino female rats and that myocardial contractility is increased as evidenced by direct measurement with the strain-gauge lever system. This instrument permits controlled alteration of the length of the attached myocardial segment as well as measurement of the tension exerted by this segment of myocardium throughout the cardiac cycle. Whitehorn and Grimmenga[11] showed that strips of the exercised cardiac muscle produced greater tension at given diastolic lengths than the control strips and they estimated that total work capacity had been elevated. Meerson and Pshennikova demonstrated that the hypertrophied left ventricles responded to clamping of the aorta with a greater increase in contractile function than that manifested by normal ventricles under the same conditions. However whether or not the minute-work capacity of the hypertrophied heart is different from that of the normal heart is questionable. Beznak demonstrated that the maximal cardiac output and the mean arterial pressure were somewhat greater in rats with cardiac hypertrophy induced by aortic constriction than in normal controls.

The studies reported here show that the physiologically hypertrophied rat heart is capable of a greater work performance than the normal heart However one should not expect all hypertrophied hearts to behave this way For instance if hypertrophy were secondary to disease, it is entirely possible that the heart might have a reduced work capacity or maximal performance because it must use part of its

Table I Developed isometric systolic tension (IST) at indicated end-dyastolic tensions

End-Diastolic tension (Gm.)	Control rats (Gm.)	Exercised rat (Gm.)	P†
5	17 00 ± 2 7	18 71 ± 2 6	> 0 1 < 0 2
10	18 30 ± 1 7	24 27 ± 2 3	< 0 001
20	18 25 ± 3 0	25 90 ± 2 2	> 0 01 < 0 05
30	18 75 ± 3 2	26 87 ± 8	> 0 01 < 0 05
40	20 16 ± 2 8	26 16 ± 3 9	> 0 1 < 0 2

Mean IST in grams, plus or minus standard errors of mean.
†P according to Fisher's t test.

Table II Mean weights of body heart liver and adrenal glands

Rats	Initial body weight (Gm.)	Terminal body weight (Gm.)	Heart weight* (Gm.)	Liver weight† (Gm.)	Adrenal gland weight (Gm.)
Control	241	274	0 901	8 26	0 062
Exercised	248	285	1 206	10 99	0 054

*0 P 08 according to Fisher t test.
†0 005 P 0 001 according to Fisher t test.

cardiac reserve to overcome the pathologic condition. In clinical surroundings, patients with compensated heart disease with hypertrophy generally have a reduced capacity for exercise in comparison with normal individuals. In response to the increased volume load which occurs during exercise, the cardiac output increases by encroaching upon the cardiac reserve. Prior to the production of hypertrophy concomitant with chronic prolonged periods of exercise, the compensating increment in cardiac output may result from an increase in heart rate and autonomic sympathetic activity, as well as ventricular distention (the Starling effect), which is accompanied by an increase in venous return and end-diastolic filling pressure. In the normal heart these various compensatory mechanisms, although they encroach upon cardiac reserve, tend to maintain an adequate circulating blood volume during acute exercise. Conversely, in the hypodynamic heart, increased demand for output may readily exceed the capacity of the heart and may lead to ventricular dilatation and failure.

Myocardial contraction represents the conversion of chemical into mechanical energy, and during each cardiac cycle the contractile mechanism must be restored to the high-energy resting state. In these circumstances, the rate at which oxygen reaches and metabolites leave the contractile units is a limiting factor in the process of attaining the high energy state. It has been postulated that the increase in the mass of myocardial fibers which occurs in cardiac hypertrophy may in some way hinder the transfer of oxygen and metabolites between blood and muscle. However, the cardiac hypertrophy produced in the present study gave no indication of ischemia; in fact, the cardiac reserve was increased. The developed IST (potential cardiac work[11,22]) was significantly greater; this indicates that when a large volume or pressure demand is placed on the hypertrophied heart, it can respond with a more pronounced Starling effect than the normal nonhypertrophied heart.

It has been shown that a gradual disturbance of the processes responsible for maintaining the contractile function in the hypertrophied myocardium may lead to the syndrome of myocardial exhaustion. The disturbances include a decrease in the concentration of desoxyribonucleic acid, reduced rate of protein synthesis, diminished adenosinetriphosphatase activity in the myofibrils, signs of degeneration and reduction in mass of the mitochondria, a slight fall in concentrations of adenosinetriphosphate and creatine phosphate, vacuolization and fatty degeneration of a proportion of the fibers and gradual atrophy of the remaining fibers, and progressive myocardial fibrosis.[11,17] However, the syndrome was not evident in this study, as there was an increase in the functional capacity of myocardial tissue. It is true that this particular study represented only the early stages of cardiac hypertrophy. Had the hypertrophy been prolonged, the syndrome of myocardial exhaustion might have been initiated. The degree of cardiomegaly produced in our study probably represents physiologic hypertrophy, since it falls below the critical heart weight of Linzbach.

Whitehorn and Grimmenga[12] found that exercised animals showed a reduced rate of growth, progressive significant bradycardia, and elevated ratios of heart weight to body weight and weight of adrenal glands to body weight. In his study, Hall[7] showed a significant increase in the weight of the adrenal glands as well as the weights of the heart and liver. In our study we found that the exercised animals showed a slight but not significant increase in the rate of growth, significant bradycardia, and a significant increase in heart and liver weights, but there was no significant change in the weight of the adrenal gland. Kratzing[23] in his study of rats which were partially immersed and swimming found no difference in the weights of the adrenal glands between the 2 groups.

Heart rates were significantly lower in the exercised animals. In human beings, a progressive reduction of the heart rate takes place during training periods of only a few weeks or months.[12-24] Richter[4] has suggested that swimming causes overstimulation of the parasympathetic system rather than the sympathicoadrenal system. If this is the mechanism, then it is

possible that the strong parasympathetic stimulation is partially responsible for the significant reduction in heart rates of the animals subjected to swimming. Cardiac arrhythmias that were due to high doses of epinephrine occurred in both groups.

Blood pressure was not significantly different between the 2 groups. The behavior of the resting blood pressure in relation to exercise habits is much less characteristic than that of the heart.[1] Other observers[26,27] have noticed a slight lowering of the systolic pressure and an elevation of the diastolic pressure in trained subjects. This suggests a paradoxical diminution of cardiac stroke volume.

Development of IST after the administration of epinephrine and isoproterenol was greater in the control animals. There was an increase in heart rate and blood pressure with a concomitant reflex bradycardia in both groups after the administration of epinephrine. The fact that the hypertrophied heart is less capable of responding to direct cardiac-stimulating drugs indicates that the myocardium may have become relatively refractory to the catecholamines as a result of the adrenal and neural releases that accompany the stresses produced by swimming. In an enlarged heart both the concentration of catecholamine per unit weight of tissue and the ability of a unit weight to take up and bind H norepinephrine from the circulation are depressed.[19,27]

The results show that swimming produces cardiomegaly in female albino rats and support the concept that the hypertrophied heart is capable of developing more tension than the normal heart; this indicates an increased cardiac work capacity concomitant with the increase in myocardial mass.

Summary

The contractile state of the intact normal and hypertrophied rat heart was investigated by measuring isometric systolic tension with a strain-gauge lever system. The myocardial tension that developed at any given end-diastolic tension is an indication of potential contractility. Cardiac hypertrophy (33 per cent) was produced by subjecting albino female rats to swimming for from 118 to 250 hours. The exercised heart was capable of developing significantly more tension than the normal heart at end-diastolic tensions of 10, 20, and 30 Cm., and the myocardial changes associated with exercise resulted in an increased ability to perform mechanical work. The development of hypertrophy concomitant with chronic exercise may represent a fundamental adaptive mechanism that is associated with long periods of increased cardiac output which acts as a compensatory measure for a tendency toward ischemia. This adaptive mechanism seems to be beneficial since no evidence was found to support the concept that hypertrophy may produce detrimental consequences. Rather, it is concluded that the degree of cardiomegaly produced in this study is advantageous in the maintenance of homeostasis during exercise. When a large volume or pressure demand is placed on the hypertrophied heart, it is actually capable of responding with a more pronounced Starling effect than the normal nonhypertrophied heart.

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Case reports

Postinfarction interventricular septal defects

Report of two cases with long survival, one with surgical repair

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Rupture of the infarcted interventricular septum has recently aroused considerable interest because of the possibility of successful surgical repair.[1-3] Accurate diagnosis of this condition has therefore become of practical therapeutic importance. The first recorded case was described by Latham in 1846.[4] In 1962 Lee and associates[5] were able to collect 220 cases from the literature. 34 cases have been reported since that time, for a total of 254 cases. Of the published cases only 17 patients underwent cardiac catheterization[1-3,7-12] and 18 of them surgical repair[1-3,13,14] with only 4 patients who survived 2 years or more.[13,15,16]

The purpose of this paper is to describe 2 patients with postinfarction interventricular septal defects in whom cardiac catheterization was performed and documented in the varying degrees of hemodynamic changes. For the first time in this entity the diagnosis was confirmed by hydrogen dilution curves and angiocardiography. One patient survived 2 years after surgical repair despite the reopening of the defect which was associated with microangiopathic hemolytic anemia. The second patient is still living 15 months after the rupture and is still asymptomatic.

Case reports

Case 1 T. B., 63-year-old Caucasian salesman was admitted to Saint Francis Hospital on April 17 1964 because of anterior chest pain of 18 hours duration. H was hospitalized 2 years previously at which time his blood pressure was 170 to 200 mm. Hg systolic and 100 to 130 mm Hg diastolic and no cardiac murmur was present.

Physical examination revealed an apical rate of 104 per minute, and the blood pressure was 102/72 mm. Hg There as systolic thrill, maximal over the midprecordium and left lower sternal border A Grade V/VI harsh pansystolic murmur was heard at the left lower sternal border and midway between the apex and the left sternal edge with good transmission toward the pex (Fig 1). The lungs were lear Serum glutamic oxalacetic transaminase (SGOT) was normal, but serum lactic dehydrogenase (LDH) was 710 units (upper limit of normal ~500 units). Serial electrocardiograms revealed changes consistent with the evolution of acute inferior myocardial infarction.

The initial hospital course was satisfactory despite light dyspnea and weakness On the sixth hospital day the dyspnea became more pronounced and bilateral inspiratory rales ere present with poor response to digitalis and diuretics. Chest films on

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Table I. Cardiac catheterization data on Patient 1 and 2

	Case 1	Case 2
O saturation ( )		
Superior vena cava (SVC)	70	82
Right atrium (RA)	70	83
Right ventricle (RV)	87	90
Pulmonary artery (PA)	86	88
Systemic artery (SA)	94	96
Pressures (mm Hg)		
RA (mean)	10	5
RV	60/13	33/4
PA	60/22 m -35	33/10 m -18
Pulmonary capillary (PC) (mean)	22	11
SA	90/60	128/82
***Blood flow** (L/M liters)*		
Systemic	6 42	11 5
Cardiac index	3 43	6 3
Pulmonary	20 76	19 2
QP/QS	3 23	1 7
***Pulmonary arteriolar resistance** (units)*	0 65	0 4

*QP QS pulmonary flow systemic flow ratio

the eighth hospital day showed pleural effusion at both bases with pulmonary congestion The heart was only minimally enlarged

On June 11 1964 right-heart catheterization was performed (Table I) and demonstrated a large left-to-right shunt at the ventricular level.

The patient was transferred to the Yale-New Haven Medical Center Preoperative chest films are shown in Fig 2 On July 23 1964 open-heart closure of a ventricular septal defect that measured approximately 1 cm in diameter was performed.

The defect was closed with five 3-0 silk sutures which were double-armed and tied over Teflon pledgets. The murmur was absent after the closure of the heart.

Postoperatively pulmonary embolism was suspected and anticoagulation started on the tenth postoperative day On the following day gastrointestinal bleeding occurred and necessitated subtotal gastrectomy and gastrojejunostomy multiple bleeding duodenal ulcers were found The patient tolerated this procedure well. A Grade III/VI systolic murmur was noted after the gastrectomy and it had the same quality and location as the preoperative murmur The patient showed no evidence of heart failure and continued to do well. Chest films (Fig 3) on Aug 24 1964 showed a normal-sized heart and normal vascular markings.

Because of persistent anemia the patient was readmitted to St Francis Hospital on Oct 24 1964 There was no evidence of heart failure. A Grade V/VI pansystolic murmur was heard. On admission, the hemocrit was 25 per cent and the hemoglobin was 7 4 gm. per cent. Several "helmet-shaped" cells, "burr" cells, and schistocytes were noted. Serum bilirubin was 2.1 mg per cent (direct 1 mg. per cent). Hemolytic process was demonstrated by the survival studies of the red blood cell. The hematologic aspects of this case will form the subject of a separate more detailed report.

The patient felt fairly well during the next 1½ years and was able to return to work for 3 hours a day He noted moderate weakness, but did not experience chest pain, dyspnea, or ankle swelling He required on the average one unit of red blood cells every 4 weeks. The cardiac findings remained unchanged

On June 13 1966 the patient reentered St. Francis Hospital with a history of recurrent episodes of pain of the right upper quadrant, chills, and fever He was deeply jaundiced There was no evidence of cardiac failure. The patient died on July 24 1966 of common duct stone cholangitis, diverticulosis of the colon and abscess of the right pelvis.

At autopsy the heart weighed 450 grams. An interventricular septal defect (8 by 6 mm.) was present in the midposterior portion of the ventricular septum (Fig 4). The defect opened through large aneurysmal dilatation (4 by 2.5 cm) in the anterior and posterior portion of the septum. The left coronary artery showed minimal atherosclerotic lesions and the right coronary artery showed 60 per cent diffuse narrowing of its posterior descending branch

Case 2 R C., 47 year-old Puerto Rican man was admitted to St Francis Hospital on Sept. 18, 1965 with the chief complaint of crushing chest pain of 18 hours duration. There was no history of hypertension On admission the pulse rate 60 per minute and the blood pressure was 210/130 mm Hg No murmur was heard there was no evidence of heart failure One hour after admission the blood pressure dropped to 60/40 mm. Hg Metaraminol infusion was started and was required for the next 14 days to maintain the blood pressure at 110/70

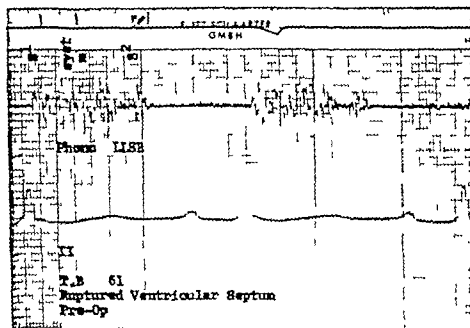


Fig. 1 Preoperativ phonocardiogram of Patient 1 (T B), recorded t the left lower sternal border showing pansystolic murmur



Fig 2 Preoperat chest -ra of P tient 1 6/16/64 showing moderate cardiac enlargement with increased lu g markings consistent ith congestive failure. Minimal left pleural effusion is present.



Fig 3 Chest -ra of P tient 1 8/24/64 with heart of normal size and clear lung fields one after closure of ruptured entricular septu

mm Hg but on 4 occasion during the first 4 day of fusion h pertensiv level were recorded for short period Antikoagula ts (heparin nd w f rin) were started on the day of admission heparin wa discontinued 2 day later Serial electrocardiograms revealed hanges of acut inferior myocardial farction. Portable hest films revealed moderate ardiomegaly SGOT w s 145 unit



Fig 4 Gross pathologic demonst tion of the ter entric la sept m of C se 1 iewed post mortem f om the opened left entricle The aneurysmal d lat tion is omposed of scar tissue and projects t the right ven ric lar hamber ending in the reopened sept l defect Not broken silk sutures partially bridging the perfor tion

On Sept 22 1965 the patient developed severe terior chest pain without dyspnea Grade IV/VI pansystolic murmur was heard and was loudest midway between the apex and the left lower ternal border The pansystolic duration of the murmur was confirmed by a phonocardiogram (Fig. 5). There was no thrill Moist râles were now heard t the right base and the liver was felt 2 fingerbreadths below the right costal margin. The patient was digitalized with good response. Metaraminol was required for the next 2 weeks. A repe t electrocardiogram showed inversion of T waves in all precordial lead with elevation of S-T segments in V and deep Q w es with S-T segment elevation and T w e in ersion in aVF II and III

The patient nderwent right heart catheterization on Nov 11 1965 (Table I) and a left-to-right h nt wa demonstrated at the right entricular level. Hydrogen dilution curves were recorded (Fig 6) nd showed an appearance time of 4 seconds in the brachial artery 3 seconds in the right ventricle and pulmonary rtery nd 12 seconds in the superior ena ca nd right atrium An table baseline accoun t for early deflections in the superior ena cava and right trial curves. The curves showed left-to-right shunt at the right entricular level. Angiocardiography was performed after the injection of 50 c. of contrast media in the pulmonary artery During the levogram, a f i t opacification of the right entricle was noted A small aneurysmal bulge was observed in the lower portion of the sept m and corresponded probably to the site of the interventricular septal defect (Figs. 7A and 7B)

After his discharge the patient course was n eventful. When he was last seen on Jan. 5 1967 he was symptomatic the blood pressure was 100/70

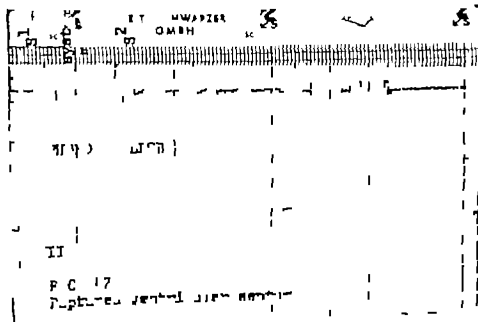


Fig 5 Phonocardiogram of Patient 2 (R. C.), recorded t the left lower sternal border showing pansystolic murmur

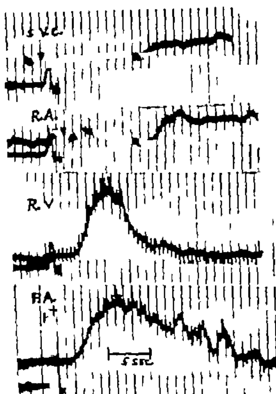


Fig. 6. Hydrogen curves of Patient 2 recorded from S.V.C. (superior vena cava), R.A. (right atrium), R.V. (right ventricle), and P.A. (pulmonary artery), showing an early appearance time of 3 seconds in the R.V. and P.A. versus 12 seconds in the S.V.C. and R.A.



Fig. 7A. Levogram of Patient 2 taken after injection of radiopaque dye in the pulmonary artery. It shows small aneurysm in the lower septum and faint opacification of the right ventricle through ventricular septal defect.

mm. Hg and the pulse rate was 96 per minute and regular. The chest was clear to auscultation and the cardiac findings unchanged. The electrocardiogram at that time revealed residual changes of old inferior myocardial infarction and chest x-ray film demonstrated mild to moderate cardiac enlargement with essentially normal pulmonary vascular markings and no significant changes since Feb. 17, 1966.

Discussion

Interventricular septal defect has been reported after 1 per cent of fatal myocardial infarction and a high incidence of coronary thrombosis has been reported.[17,4] Our first patient was unusual since only moderate but diffuse stenosis of the posterior descending branch of the right coronary artery was found. The site of the perforation was in the lower part of the septum in 66 per cent of the cases. According to Lee each patient with prolonged survival had findings that suggested or established

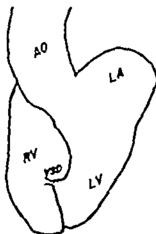


Fig. 7B. Diagram of Patient 2 to illustrate the filling of right ventricle (RV) from the left ventricle (LV) by way of ventricular septal defect (VSD); ascending aorta (AO) and left atrium (LA) are identified.

the presence of aneurysm; moreover, an aneurysm was present in 4 of the surgically corrected group.[7] Our 2 cases showed small aneurysms around the defect. The rupture usually occurs between the third to twelfth day (average 7.4 days).[19] However, this occurred on the first day, as observed in our first patient, in 21 per cent of 90 patients who were reviewed by Oyamada and Queen.[13]

Of the contributing factors, hypertension is probably the most significant.[20-22] One of our 2 patients was known to be hypertensive and the second was hypertensive on admission.

Clinically, septal rupture is manifested by rapid deterioration of the patient's condition, as in Patient 2, with onset or worsening of chest pain, shock, and heart failure.[7] A loud pansystolic murmur is heard and in 62 per cent of the cases, a thrill is present.[4] Unlike the murmur of congenital ventricular septal defect, which is usually louder at the left sternal edge, the murmur of ruptured septum is usually maximal midway between the left lower sternal border and the apex.[23] The location of the murmur, which is related to the apical site of the perforation, makes it sometimes difficult to rule out mitral insufficiency.

In the differential diagnosis, rupture of the papillary muscle should be considered; this is characterized by severe pulmonary edema and an apical systolic murmur without a thrill which is often accompanied by a diastolic murmur. Papillary muscle dysfunction[24] results in a diamond-shaped late systolic murmur. In mitral insufficiency secondary to left ventricular dilatation the murmur is apical in location and has a more gradual development. In tricuspid insufficiency, the murmur increases with inspiration.

The electrocardiogram is not diagnostic of rupture. The reported changes include evidence of septal infarction, right bundle branch block, and atrioventricular block.[7] Our second patient showed evidence of both inferior and anteroseptal infarction whereas the first patient showed only inferior infarction as reported by Sanders and associates[17] in 4 out of 31 cases. Chest films usually show generalized cardiomegaly and increased pulmonary vascular markings.[4] Hemodynamically, the defect adds the load of a left-to-right shunt to an already damaged myocardium.

We believe that the diagnosis should be confirmed by cardiac catheterization because atrioventricular insufficiency may mimic septal rupture. The magnitude of the left-to-right shunt and pulmonary artery pressure should be determined before subjecting the patient to surgery because, as in our second patient, a minimal shunt with normal pulmonary artery pressure is usually well tolerated. Cardiac catheterization has been performed in 19 patients, including 8 reported by Borcourt and colleagues, our 2 cases, and others.[illegible] No complications have been reported during the procedure. Data of oxygen saturation were diagnostic of a left-to-right shunt at the right ventricular level in all patients except one.[1]

The ratio of pulmonary to systemic flow varied between 1.5 to 5.5 with an average of 2.8, which indicates a moderately large shunt. As a consequence of heart failure, the mean right atrial and pulmonary wedge pressures were elevated and averaged 8 to 13 mm. Hg, respectively. There was moderate pulmonary hypertension with an average pulmonary artery systolic pressure of 62 mm. Hg. Data that allowed measurement of pulmonary arteriolar resistance were available in 7 patients and revealed a slight elevation (average 2.2 units of resistance). This would indicate that acute shunts are not usually accompanied by significant increase in pulmonary vascular resistance.

Indicator dilution methods may be used to confirm the diagnosis, particularly when oxygen saturation data are equivocal. Peripheral sampling has been reported by a few authors.[7,23,26] Jacobs and colleagues[1] were the first to use the more diagnostic central sampling in this entity by injection of indocyanine green dye in the right pulmonary artery with simultaneous sampling from the right ventricle and femoral artery. To the best of our knowledge, Case 2 is the first report of the use of hydrogen curve in ruptured septum. The accuracy and simplicity of this method, which requires only one catheter in the right heart, has been fully documented[26] and would make it highly suitable in these critically ill patients.

Case 2 is also the first report of the use of angiocardiography with a demonstration of the location of the defect and of a small aneurysm. It is possible that left ventricular catheterization may result in the dislodgment of intramural thrombi particularly in the immediate postinfarction period and for that reason pulmonary artery injection may be less hazardous. Fifty cubic centimeters of dye were injected in our case but a larger quantity would appear to be required for optimal visualization. Angiocardiography is helpful in demonstrating the defect and its location as well as multiple ruptures, which occur in 40 per cent of patients with long survival. Concomitant ventricular aneurysms can be visualized by contrast studies and probably require excision for optimal results.

The prognosis is most ominous: 46 per cent of the patients die within the first week, 87 to 89 per cent during the first 2 months,[17] and 93 per cent during the first year. The patients with long survival have varying degrees of heart failure. Survival of 15 months with absence of symptoms, as in our Case 2, is unusual. The longest survival (13 years) was reported by Landale and associates.[17]

This bleak outlook would justify surgical repair of the perforated septum. The first surgical attempt was made by Cooley and colleagues[1] in 1957 and so far 19 examples of surgical experiences, including our patient have been reported.[12] The defect was repaired under direct vision in all the patients except one[2] and a prosthetic patch was used in 8 patients.

It is generally felt that preferably 3 to 6 months should elapse after a myocardial infarction before surgery is undertaken; at an earlier date the infarcted septum would not hold the sutures. However Allen and Woodwark[3] have repaired a defect 12 hours after rupture and Cramer and associates[4] have repaired a defect 24 days after rupture with survivals of 15 months and 9 months respectively when reported. Operation can be delayed, preferably for 3 months, in those patients who respond initially to medical management are shown to have a significant left-to-right shunt and continue to be limited physically (Case 1). In a third group of patients (represented by Case 2) who respond well to medical therapy and who have a small shunt surgery is not definitely indicated. Of the 19 patients who underwent surgery only 4 including our patient have survived two years or more after operation.

Our patient (T.B.) developed microangiopathic hemolytic anemia after the partial reopening of his defect. He represents the first report of this syndrome that occurred with reopened acquired ventricular septal defect.

Summary and conclusion

Two cases of rupture of the interventricular septum due to acute myocardial infarction are reported. They differed symptomatically and hemodynamically and required different management. The first patient underwent surgical repair and survived more than 2 years despite the reopening of his defect and the development of microangiopathic hemolytic anemia. The second patient had a small left-to-right shunt and was asymptomatic 15 months after rupture.

Emphasis is placed on early clinical diagnosis of this condition with confirmation by cardiac catheterization. The value of hydrogen curves and angiocardiography is stressed. Criteria for surgical correction are discussed.

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Sinus arrest in proximal right coronary artery occlusion

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As pointed out by James and others, supraventricular arrhythmias complicating a recent myocardial infarction frequently are the result of the infarction extending into the atrial walls. In some cases, such arrhythmias are a consequence of ischemic lesions of the sinus node. Besides implying important therapeutic consequences, the recognition of these types of sinus node lesions may give a clue to the site of coronary occlusion

In the following we present 2 cases of posterior myocardial infarction complicated by sinus arrest and A V nodal escape rhythm which indicates a proximal right coronary artery occlusion

Case reports

Case 1 J A 69-year-old man, died of acute myocardial infarction complicated by disturbances in cardiac rhythm. During the last 10 years he had suffered from moderate angina pectoris. His terminal illness started 4 days before death with severe precordial pain that lasted for several hours, and hich was followed by ertigo and syncope On the same day of admittance ECG showed posterior myocardial injury and normal sinus rhythm During the next hours he had attacks of bradycardia and h potension ECG showed slow A-V nodal rhythm (Fig 1) Administration of metaraminol and isoproterenol was followed by restoration of sinus rh thm and normal blood pressure. Relapses ere treated in the same with the same result The day before he died, the patient developed trial fibrillation.

At autopsy there as an old occlusion of the left anterior descending coronary artery that corresponded t an old anteroseptal myocardial infarction. The right coronary artery which crossed the crux was in its proximal part (ithin 1 5 cm from the ostium) markedly narrowed by sclerosis and occluded by fresh thrombus. The sinus node artery which arose at this point, was also occluded by the thrombus. Corresponding to the right coronary artery occlusion there was recent myocardial infarction that involved the posteroseptal part of the left entricle, the right ventricle free wall, and the right atrium The sinus node was extensively infarcted (Fig 2,*A* and *B*). The A V node and A V bundle were intact.

I this patient the sinus node lesion was clinically evident from the sinus arrest with A V nodal rhythm and proximal right coronary artery occlusion was, therefore, anticipated The alternating sinus- and A V nodal rhythm can best be explained by a varying degree of sinus node ischemia—improved oxygenation being induced by sympathomimetics.

Case 2 E.S an 85-year-old woman had been suffering from syncopal ttacks for several years On admittance she was severely ill with arterial hypotension and bradycardia. ECG showed posterior myocardial injury and slow A V nodal rhythm (Fig 3). Administration of isoproterenol was followed by increased heart rate but only transient rise of blood pressure The patient died 20 hours fter admission.

At utopsy the coronary arteries showed con-

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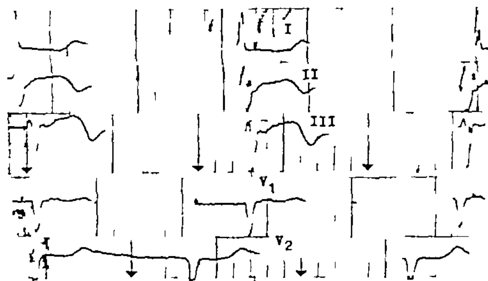


Fig. 1. Case 1. The ECG recorded 2 hou fter adn ssion, how posterior myocardial injury and slow A V nodal escape rhythm

Fig. 2. Case 1. A. Microphotograph of the sinus node lesion. Transverse section of the sinus node artery (top). The sinus node is seen to the right and below the sinus node artery. The subepicardial fat with hemorrhage is seen to the right, and the atrial wall on the endocardial side to the left. B. Detail from A shows necrotic myocardial fibers and granulocyte infiltration in the sinus node.

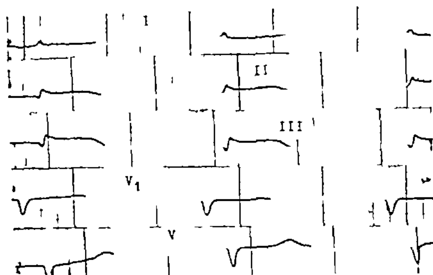


Fig 3 Case 2 The ECG recorded t admission show posterior myocardial injury and slow A V nodal escape rhythm.

Fig 4 Case 1 Microphotograph of the sinus node ith trans erse sect on of the sinus node artery (top) The sinus node is seen bet een the epicard um (right) and the right atrial all (left and below). B Detail from A show necrotic myocardial fibres nd granulation in the sinus node (right) and the right trial all (left)

fluent therosclerosis. A fresh thrombus in the proximal part of the right coronary artery occluded the ostium of the sinus node artery. There was an old myocardial infarction in the right atrium including parts of the sinus node. Signs of recent infarction were found in the right atrium in the posterior wall of both ventricles, in the sinus node and A-V node, but not in the A-V bundle (Fig. 4A and B).

In this case an occlusion of the right proximal coronary artery was anticipated from the clinical and electrocardiographic signs. The former syncopal attacks in this patient may have had some relation to the old myocardial infarction of the right atrium including parts of the sinus node.

Comment

The clinical syndrome demonstrated by these 2 cases is characterized by (1) an acute posterior myocardial infarction complicated by (2) transient or permanent sinus arrest with (3) an escape rhythm from a lower cardiac center. In our cases, the sinus node artery originated from the right coronary artery, which was the site of a recent proximal occlusion. Corresponding ischemic lesions were found in the posterior wall of the left ventricle, the lower posterior parts of the right ventricle, and in the right atrium including the sinus node.

Depending on the collateral circulation, a sinus node lesion that follows occlusion of the sinus node artery may show all degrees of severity from transient ischemia to total necrosis. The resulting impairment of the sinus node function may be transient or permanent. The sinus node lesion in our cases lead to sinus arrest with slow A-V nodal rhythm and arterial hypotension which was probably related to the bradycardia.

Discussion

Proximal occlusion of the right coronary artery is the most common cause of ischemia of the sinus node. In 60 per cent of the population the sinus node artery (ramus ostii cavae superioris) originates from the right coronary and always from its proximal 2 to 3 cm. In the remaining 40 per cent it originates from the left coronary artery and then most frequently within 1 cm, more seldom 4 to 5 cm from the origin of the circumflex artery (Fig. 5).[4] Obstruction of the sinus node artery leading to damage of the sinus node is therefore not

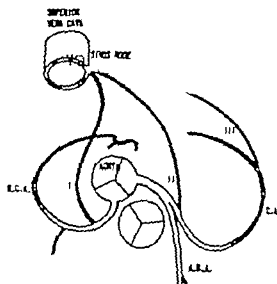


Fig. 5. The diagram of the coronary artery anatomy shows the alternative origins of the sinus node artery. I. Sinus node artery originating from the proximal part of the right coronary artery (approx. 60 per cent of cases). II, III. The two most common origins of the sinus node artery from the left coronary artery (approx. 40 per cent). A.D.A. Anterior descending artery. C.A. circumflex artery. R.C.A. right coronary artery.

limited to occlusion of the right coronary artery. When occlusion in the proximal part of the left coronary is the cause of sinus arrest, the corresponding myocardial infarction will in most cases be localized to the lateral wall of the left ventricle.

James has shown that atrial arrhythmias in acute myocardial infarction often are caused by ischemic lesions of the sinus node and therefore indicate occlusion of the sinus node artery. Various types of arrhythmias have been described.[1-13] Our cases seem to belong to a separate group characterized by slow A-V nodal rhythm. This rhythm may be misinterpreted as atrial fibrillation if attention is not paid to the constant RR interval or signs of retrograde atrial conduction. In our cases we have thus been able to demonstrate the nodal rhythm.

The A-V node has a double arterial blood supply, but the main node artery originates from the artery crossing the crux cordis, most frequently the right coronary.[12] A proximal right coronary artery occlusion may therefore also lead in some cases to ischemic lesion of the A-V

node. Thus was seen in Case 2 where both the sinus node and the A V node were infarcted. In such a case the accompanying A V node lesion cannot be clinically diagnosed (by demonstrating A V block) if the sinus node function is not restored

Clinically a distal occlusion of the right coronary artery that leads to a posterior wall infarction and A V node lesion can be misinterpreted as the syndrome following right proximal occlusion in that both show bradycardia. In distal occlusion however the bradycardia is due to A V block and normal P waves can be demonstrated

Electrocardiographically it is not possible to distinguish between sinus node inactivation (sinus arrest) following structural or circulatory damage of the sinus node and functional blocking of the sinus node impulse (S-A block) Sinus block is transitory in most cases of short duration and may be caused by various stimuli (e g strong vagal effect) Sinus arrest is usually of longer duration, but not necessarily permanent as in cases with reversible or incomplete damage of the sinus node Several factors can contribute to sinus node failure and it may be difficult to evaluate their relative importance. When the type of sinus node lesions demonstrated at autopsy is considered, it seems less probable that vagotonia or other functional factors have been of major importance in the pathogenesis of the sinus arrest in our cases. If present electrocardiographic signs of atrial infarction may strengthen a clinical suspicion of sinus node damage.

When an acute myocardial infarction is complicated by an atrial arrhythmia, which indicates sinus node ischemia it is occasionally possible to determine the accurate site of the occlusion by combining knowledge of the coronary artery anatomy and the electrocardiographic localization of the infarction In the cases that we have presented we have predicted the occlusion of the proximal part of the right coronary artery which was found at autopsy In some patients with the same rhythm disturbances who survived their posterior myocardial infarction with restoration of the sinus node function we have in the same way suspected a proximal right coronary artery occlusion to be present. However in patients with a history of long-standing coronary illness former occlusions of the coronary arteries may be a source of diagnostic error

In an autopsy series of 66 consecutive patients who died from acute myocardial infarction in Aker hospital we have found 4 cases (6 per cent) with recent proximal occlusion (within 3 cm from the coronary ostium) of the right coronary artery Only one of these 4 cases had clinical signs of impaired sinus node function In this case ECG showed posterior myocardial injury and A V nodal rhythm which indicated the right proximal coronary artery occlusion. In the cases that lacked clinical signs of sinus node lesion the proximal right coronary artery occlusion was not accessible for clinical diagnosis. In such cases, either the sinus node artery does not originate from the occluded right coronary or the sinus node has a sufficient collateral blood supply to maintain pacemaking

An accurate clinical localization of a coronary occlusion does not have any great practical importance at the present time. However the diagnosis of sinus arrest following sinus node artery occlusion is mandatory as a basis for rational therapy Decrease of the coronary blood flow that follows bradycardia with arterial hypotension and low cardiac output, may lead to myocardial acidosis conduction disturbances and appearance of ectopic pacemakers with tachy-arrhythmias. In the treatment of our patients with sinus arrest secondary to sinus node artery occlusion we have strived to increase cardiac output and coronary blood flow by *increasing the rate of the nodal escape rhythm* Increased coronary blood flow may in time restore sinus node function in cases where *the sinus node lesion is not complete*

Beta adrenergic agents increase heart rate and cardiac output, improve myocardial oxygenation and thereby will contribute to restoration of the sinus node function.[14] The direct stimulating effect of these drugs on the sinus node itself would also be expected to be of some value. Artificial pacemaking may be a valuable therapeutic aid in the treatment of sinus arrest following sinus artery occlusion

Summary

Two cases of a clinical syndrome following proximal right coronary artery occlusion with occlusion of the sinus node artery are presented. This syndrome is characterized by (1) acute posterior myocardial infarction complicated by (2) transient or permanent sinus arrest with (3) an escape rhythm from a lower cardiac center.

The ischemic lesion that corresponds to this clinical syndrome is localized in the posterior wall of the left ventricle, in the lower posterior parts of the right ventricle, and in the right atrium including the sinus node.

After a review of the coronary anatomy related to this syndrome is made, the diagnosis of the condition is discussed. The opportunity of localizing clinically the exact site of the coronary occlusion is pointed out. The importance of recognizing the *sinus arrest, which requires special attention* and therapy, is stressed. Treatment is discussed briefly.

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Single coronary artery

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A single coronary artery represents a rare congenital anomaly. Recent case reports[1-4] have brought the total number to 79 reported cases. Some of the initial reports are fragmentary with clinical histories that are inadequately documented and the details of the variations in vascular pattern are vaguely outlined. Postmortem coronary injection techniques have been used in only 4 other cases[4] to define specifically the variation of a single coronary artery and anastomotic channels.

Case report

This 71-year-old Caucasian man was admitted to Little Rock Veterans Administration Hospital on March 25, 1966. He was complaining of orthopnea, dyspnea on exertion, chronic productive cough, and wheezing for many years. Because of the dyspnea, the patient had retired several years prior to admission and had been hospitalized numerous times for episodes of dyspnea and productive cough. Occasionally he had a "tight feeling" in his chest that was usually related to exertion. Intermittent anorexia and weight loss of 15 pounds had occurred in the 6 months preceding admission.

Physical examination revealed a chronically ill, short, slender patient who was coughing and being. He was 63 inches tall, and weighed 92 pounds. His temperature was 99.2°, his pulse rate was 100 and irregular, and his blood pressure was 135/70 mm. Hg. Pertinent findings were limited to the chest. There was increased resonance to percussion, breath sounds were distant, and a few râles and ronchi were heard throughout the chest. There was no evidence of cardiomegaly or murmurs.

Laboratory studies disclosed a leukocytosis; the leukocyte count was 12,400 with a differential showing 86 per cent immature cells, which is compatible with lymphosarcoma. Hematocrit was 31, hemoglobin was 10.6 Gm. per cent, reticulocyte count was 0.3 per cent, and the platelet count was 116,000. A subsequent blood count revealed increasing leukocytosis, with 96 per cent immature cells and a platelet count of 86,000. Arterial blood gases showed pH of 7.404, pO_2 47 mm. and pCO_2 of 43.0. A chest x-ray film revealed a normal-sized heart with evidence of pulmonary fibrosis and emphysema. The electrocardiogram is shown in Fig. 1.

Clinical Course. The patient continued to have severe respiratory distress and fever. He was placed on bronchodilators, fluids, and antibiotics for the treatment of chronic obstructive bronchitis. He was also digitalized because of a tachycardia of 150 and extreme dyspnea. Generalized bleeding from mucous membranes and gastrointestinal tract developed. Before he died he lapsed into a coma, continued to have respiratory distress, and became markedly febrile.

Autopsy findings revealed a cachectic man with numerous areas of hemorrhage in the skin and mucous membranes. Evidence of advanced chronic bronchitis and emphysema was present. Bone marrow and spleen sections revealed evidence confirmatory of lymphosarcoma.

Examination of the heart revealed a normal external appearance, and a weight of only 252 grams. The left ventricular wall was 10 mm. and the right ventricular wall was 3.5 mm. in thickness. The valves were normal. The aorta was pliable and minimal atherosclerotic plaques were noted. Only the right coronary orifice was evident; there was a dimple present in the area of the normal left coronary ostium. The right coronary ostium was 6 mm. in diameter. This artery bifurcated 8 mm. from the orifice into 2 rather large arteries. The modified

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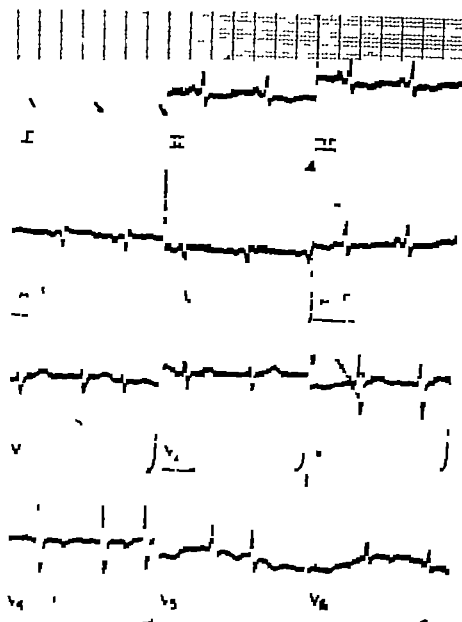


Fig. 1. Electrocardiogram on reported case. Rate: A, 100 V 100. PR interval, 0.12 sec. QRS, 0.08 sec. This electrocardiogram is abnormal, ho ing occasional premature trial contractions and nonspecific ST and T-wa changes.

Schlesinger technique was used o inject the artery with cannulas which were placed in each of the 2 large arteries as shown in Fig. 2. The 2 large arteries assumed parallel course for cm, with one continuing in the course of the normal right coronary artery. The other artery subsequently divided into 3 branches as it coursed anteriorly across the right ventricular surface, occupying the area usually supplied by a branch of the normal right coronary artery. These 3 arteries subsequently joined vessels which occupied the position of the normal anterior descending artery as one can see on the x-ray film. Branch A emptied into a slightly enlarged tortuou

hannel nd one would assume there was retrograd filling of this essel. Branch B supplied the myocardium in a local area as show n, and contributed t the vessels filled from Branches A and C. Branch C appeared t supply blood t the vessel occupying the terminal portion of the usual anterior descending branch. Careful dissection revealed a fibrous band 6 mm. in length and 1 mm. in diameter extending from the site of the usual bifurcation of the lef coronary into the anterior descending and circumflex branches and extending to the aorta (Fig. 3), being ttached externally opposite the previously described dimple in the left aortic sinus. Section of the fibrous band

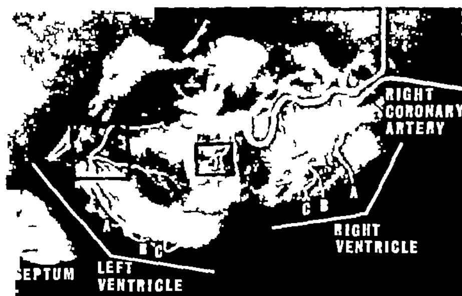


Fig 2 A postmortem arteriographic injection of the 2 major branches of the single right coronary artery is show The area of the fibromuscular structure which extends from the aorta to the coronary vessel (Fig 3) and area of collateral essels (Fig 4) is outlined.

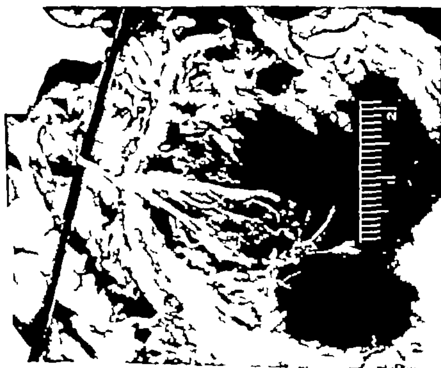


Fig 3. Enlarged iew of rea outlined in Fig 2

revealed a tubular structure of cardiac muscle with an eccentrically located arterial vessel approximately 50μ in diameter. Studies with the use of Masson and Elastic stain confirmed the fibromuscular structure. Several sections were taken through the aortic dimple and no ostium was found. Gross collateral vessels of 0.3 and 0.4 mm. were demonstrated between the terminal branches of the right coronary and vessels that occupied the position of the usual circumflex branch (Fig. 4). Significant atherosclerotic lesions were noted at the ostium of the right coronary orifice, in the proximal portion of the 2 major branches, and in the area of the crux. None of these lesions occluded more than 25 per cent of the lumen of the artery at any site. The myocardial sections showed normal cardiac muscle.

Discussion

The progress of surgical repair of complicated congenital anomalies and the advent of coronary angiography have been a stimulus for the detailed understanding of the anomalies of the coronary arteries. Blake and associates and Edwards and associates have divided the anomalies of the coronary arteries into those of major and minor significance. The major division includes anomalous origin of the coronary artery from the pulmonary trunk and coronary fistulas which serves as a life-sustaining communication as a venous-artery shunt or more frequently an arteriovenous or arterio-left heart fistula. Abnormalities of number, origin, size and distribution are considered with the minor division. There are frequently more than 2 coronary arteries but the so-called accessory arteries are usually small, frequently overlooked in routine dissection, and frequently originate in the right aortic sinus.[10,11] A single coronary artery, however, is a rare finding and the embryogenesis not well understood.[12] In approximately one third of the cases reported a single coronary artery has occurred in association with other serious congenital abnormalities. This accounts for the high incidence and approximately 50 per cent mortality rate of reported cases under 20 years of age. Except for the complicating congenital lesions, a single coronary artery is compatible with longevity, the oldest reported subject was 80 years of age.[13] Nine of the adult cases have been associated with myocardial ischemia or infarction.[3] Many of the adult cases have been asymptomatic and the anomaly was appreciated only at post mortem examination as was true in the present case.

The importance of preoperative appreciation of the coronary vascular pattern in complicated congenital heart disease has been increasingly recognized.[14] At least 3 cases have been reported in which



Fig. 4. Enlarged view of area outlined in Fig. 2.

surgical ligation of the single coronary or significant branches of a single coronary artery such as through a right ventriculotomy was a contributory factor in the death of the patient.[17]

The muscular tubular structure which extends from the external surface of the aorta opposite the aortic *dimple* to the coronary vessels as shown in Fig 3 has not been previously described. This structure could represent an atretic coronary artery with an extremely small lumen (50μ) or possibly a capillary vessel within a tubelike structure of cardiac muscle. The fact that this tubular structure was well defined and contained a moderate amount of connective tissue seems to make the former possibility the most likely. The significance of this observation to the embryogenesis of a single coronary artery remains to be determined but we believe that for some reason the left coronary anlage failed to develop in this patient.

Summary

The case of an adult with a single coronary artery is discussed and detailed post mortem arteriographic and pathologic findings are presented. *The classification of* coronary anomalies is outlined briefly. Attention is directed to the need for increasing recognition of coronary anomalies in the proper angiographic evaluation of both congenital and acquired heart disease.

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Clinical pathologic conference

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Clinical abstract

DR. LAUER: On February 12, 1966, a 62-year-old Caucasian man was admitted with the chief complaint of marked shortness of breath and diaphoresis accompanied by weakness and dizziness of several hours' duration. Shortly before admission the patient was seen by his private physician who noted a blood pressure of 100/70 mm. Hg, a weak pulse at 96 per minute, cyanosis, and bilateral distant breath sounds. There were no neurologic signs. The patient was given oxygen and sent to this hospital.

Past history. During his childhood the patient had had poliomyelitis, which affected one leg and later necessitated surgical correction of a resultant deformity. He grew normally and developed into a well-built and muscular young man. When he was about 25 years old, he complained of frequent stomach trouble. He collapsed occasionally after work although he was not performing any heavy physical labor; his complaints were attributed to psychological causes. When he was 30 years old, he began to complain of coldness of the legs and to experience difficulty in standing and walking; there was no definite history of intermittent claudication. His legs were extremely painful at night, and often prevented him from sleeping. At times, he was unable to tolerate the weight of even a light blanket on his legs. His legs had to be warmed by heating lamps which were kept at carefully regulated temperature because he could not feel even intense heat and could sustain burns very easily. During that period many of his complaints were attributed to personality problems although at one time, the diagnosis of Buerger's disease was made and he was advised to stop smoking. In his late thirties he began to develop ankle ulcers which healed with local treatment and "whenever he stopped smoking." Later his symptoms were attributed to varicose veins; on several occasions, he was treated for thrombophlebitis. In 1943 he was admitted to a large teaching hospital where bilateral high femoral vein ligation was performed and he received numerous local injections.

During the next 10 to 15 years the leg ulcers reopened repeatedly and healed with local treatment and plaster casts, but it became progressively more difficult to control them. He was often bedridden and inactive, complained continuously of leg pain and his toes became cyanotic. There was an apparently striking discrepancy between his muscular physical appearance and his unwillingness to walk, stand, or do any physical work. He was hospitalized on several occasions. There was no history of chest pain, congestive heart failure, or diabetes. His recurrent gastrointestinal complaints became more consistently associated with regurgitation of food and vomiting after large meals. In 1965 he was again treated by a private physician for leg ulcers. At that time, examination revealed marked scarring and induration of the skin and subcutaneous tissues of the lower legs, as well as contractures and large ulcers over the ankles. The dorsalis pedis pulses were weak but palpable but the pulsation of the posterior tibial arteries could not be palpated because of the ulcers. Both femoral pulses were present. Oscillometric readings were as follows: above the right ankle, 2+; above the left ankle, 4+; below both knees, 6+. There were no measurements of the blood pressure available in the records. After temporary improvement the ulcers recurred and persisted. In June, 1965, the patient collapsed suddenly at work and was admitted to a small community hospital. The diagnosis of a small stroke was made and a slight, persistent, facial paralysis was noted. There was no hypertension discovered, and there were no symptoms referable to his heart. *He refused further investigation and was discharged to the care* of his private physician who last saw him on February 8, 1966. Four days later he was admitted to Jewish Memorial Hospital.

Physical examination revealed an acutely ill, elderly Caucasian man who was conscious but very

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restless and anxious, pallid cyanotic profusely diaphoretic, and complaining of epigastric pain. Blood pressure was once recorded at 50/0 mm. Hg but it remained unobtainable thereafter. Respirations were 16 per minute and radial pulses were unobtainable. Pupils were equal there were bilateral cataracts. There was neither nuchal rigidity nor any neurologic sign. Neck veins were distended. Examination of the chest revealed bilateral crepitant râles. Auscultation of the heart showed regular rhythm at 100 per minute the heart sounds were very distant and no murmurs were audible. The abdomen was soft and not distended the liver was palpable three fingerbreadths below the right costal margin, and the spleen was not felt. Rectal examination revealed no evidence of gross bleeding. The feet were edematous and the toes were cyanotic. Both lower legs were covered by plaster casts. There were no femoral pulses felt.

Hospital course. Despite oxygen and intravenous norepinephrine the patient remained in shock. Hemoglobin was 11.6 Gm. hematocrit, 36 per cent white blood count, 6,600. At 2 A.M. on the day following admission a faint radial pulse was detected on the left however the patient remained cyanotic had cold, clammy skin, and was extremely restless. At 5 A.M. the heart sounds were somewhat stronger and an apical systolic murmur was heard. The patient died at 9:15 A.M.

Discussion

DR. ROSNER. On the surface the problem appears to be a case of a 62 year-old man with acute cardiogenic shock. The electrocardiogram reveals a current of injury in Leads II III and aVF, with reciprocal S-T depression across the precordium a QS in V1-3 and Q waves in Leads II III and aVF as well as a right bundle branch block (Fig. 1). Without serial tracings we cannot be certain that this represents an acute myocardial infarction. However we can be sure that the patient has suffered myocardial infarctions of both the anterior and posterior walls the acute ischemic changes may represent fresh myocardial infarction or acute coronary insufficiency perhaps accompanying acute circulatory failure.

DR. COLIN J PIGOTT The serum glutamic oxalacetic transaminase (SGOT) was elevated at 530 units, but the specimen was hemolyzed the lactic dehydrogenase (LDH) was 480 units.

DR. ROSNER. Since his liver was congested in acute congestive heart failure the SGOT already rendered suspect by hemolysis may have been elevated somewhat without reflecting acute myocardial infarction however in conjunction with the electrocardiocardiogram I think this very marked elevation does indicate probable acute myocardial infarction. It was probably too early for elevation of the LDH however the normal value is somewhat against pulmonary embolism and infarction.

I would like to disregard the precipitating

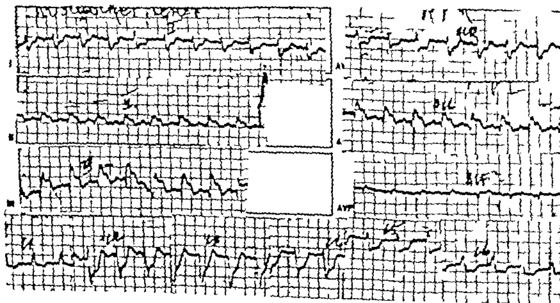


Fig. 1. Electrocardiogram taken on admission to hospital.

cause of death in this patient and to discuss his basic illness. We are told that from the time he was 30 years of age he had severe coldness of the legs and had difficulty when standing and walking. During the ensuing 10 to 15 years he developed cyanosis of the toes and ankle ulcers. He was thought to have thrombophlebitis on several occasions and was treated for varicose veins. The diagnosis of Buerger's disease was considered. Though the patient's ankle ulcers healed when he stopped smoking, there is no mention either of vascular disease in the upper extremities or of gangrene. The dorsalis pedis pulses were palpable in 1965 and the oscillometric readings were much better than would be expected from the extensive scarring and the induration that were described then. Moreover, he had cyanosis of the toes for many years. We are forced to explain definite persistent distal cyanosis in the lower extremities which was accompanied by apparent ischemic changes without obvious obstructive disease in medium-sized arteries. Though the venous stasis occasioned by his varicose veins may have potentiated the cyanosis, the long-standing rest pain and coldness speak for arterial insufficiency. It is conceivable that a combination of arterial disease on the basis of premature arteriosclerosis and venous insufficiency due to varicose veins or Buerger's disease could produce this picture, but the indirect evidence for arterial disease is not supported by examination of the arteries to the affected limbs.

We are also informed that, in his middle twenties, the patient collapsed frequently after work and that he often complained of stomach trouble, particularly after large meals.

DR. LAUER: That point was one that interested those of us who saw him. We had wondered whether this implied multisystem involvement indicated a long standing panarteritis such as polyarteritis nodosa.

DR. ROSNER: Certainly polyarteritis nodosa frequently affects the heart, the brain and the gastrointestinal and musculoskeletal systems. We have evidence of ischemic heart disease, presumptive evidence of episodes of cerebral ischemia as represented by his history of collapse and an eventual small stroke and, perhaps, mesenteric artery ischemia in view of his gastrointestinal



Fig. 2. Chest x-ray taken on admission to hospital.

complaints after large meals. I rather doubt mesenteric artery ischemia in view of the very long course and the lack of pain. I would be more suspicious of local esophageal or gastric lesions. Moreover, the prominence of his ischemic peripheral vascular disease in this picture is unusual even for the protean manifestations of polyarteritis nodosa, and once again I must pause with the lack of evidence of an obstructive disease of the arteries to the lower limbs.

It would seem then that we must explain apparent arterial insufficiency adequate to cause severe ischemia to the lower extremities on some other basis than disease of medium-sized arteries.

At this juncture I think fresh clues will be provided by considering the portable chest x-ray film (Fig.). We are certainly not surprised to see marked central venous congestion consistent with congestive heart failure with infiltrative changes that suggest pulmonary edema. But there are other findings which are extremely provocative. The heart is not only enlarged but there is marked enlargement of the left ventricle of the type seen in hypertension. The aortic

knuckle is elongated and the whole aortic shadow is widened with particularly interesting widening of the proximal part of the descending aorta which gives a double-knuckle appearance. When one sees this elongated knuckle there usually is suspicion of dilatation of the left subclavian artery and the double-knuckle appearance is attributable to poststenotic dilatation. In addition, there is very suggestive loss of continuity of bone on the inferior margin of the eighth and seventh posterior ribs I think these could well be described as "notching (Dock's sign) In short I believe this x-ray film demonstrates coarctation of the aorta and I think that was the patient's basic problem

DR. LAUER We were somewhat suspicious of aortic disease but not of coarctation we suspected a dissecting aneurysm of the aorta. If you think coarctation of the aorta is the main diagnosis, aren't you disturbed by the lack of hypertension in the upper extremities.

DR ROSNER It is true that no radial pulse was palpable during his brief tenure in this hospital but he was in shock and I do not feel that we have any findings that indicat selective closure of vessels, nor is there a history of the characteristic pain which accompanies an acute dissecting aneurysm of the aorta. With regard to the absence of hypertension in the upper extremities, we have no direct observations since he was in shock on admission here All we know is that there was no hypertension present in 1965 at the aforementioned small community hospital By that time he had suffered a small stroke and very probably at least one myocardial infarction. Another possibility is that he had aortic stenosis coexistent with coarctation of the aorta, a not infrequent association However it is difficult to believe that aortic stenosis of a degree sufficient to prevent apparent hypertension in this man would have been overlooked during his numerous hospitalizations. I think that he was probably thought to have essential hypertension which was cured after a myocardial infarction The rest of his clinical picture is consistent with the diagnosis of coarctation of the aorta which includes the cerebral manifestations. Manifestly the cyanosis of his lower extremities was not attributable to reversal of blood flow through a patent ductus arteriosus since this occur only in the infantile type of coarctation and is compatible with only a few years of life In the adult postductal type there is slowed blood flow to the lower extremities sufficient in 5 per cent of cases in one series to cause intermittent claudication If we correlate this with the poor venous return from his legs because of the severe varicose veins and repeated thrombophlebitis, we have adequate explanation for the cyanosis and the other evidence of severe circulatory insufficiency to his lower extremities.

DR. LAUER Do you consider that the patient had a coarctation of the abdominal aorta and/or supravalvular aortic stenosis and what do you consider the immediate cause of death?

DR. ROSNER The abnormalities of the aortic arch which I described on the chest x-ray films are found neither in the abdominal kind of coarctation nor in supravalvular aortic stenosis, nor is rib notching usually present, though it may be present in the last 2 or 3 ribs. Further the only murmur that was described was an apical systolic murmur which would be consistent with the usual adult variety of coarctation whereas, in the abdominal type a murmur is best heard over the lumbar spine or anteriorly through the abdominal wall. As for the immediate cause of death I think we have adequate evidence for extensive atherosclerosis and previous myocardial infarction and I presume that an acute myocardial infarction was the probable cause It is quite possible that he had mural thrombi from at least 2 previous transmural myocardial infarctions and he may have had an acute cerebral embolus but there were no neurologic signs. I conclude that the immediate cause of death was an ordinary acute myocardial infarction in a man whose extraordinary disease was coarctation of the aorta.

D Rosner Diagnoses coarctation of the aorta acute myocardial infarction old anterior and posterior wall infarctions, mural thrombus, and generalized atherosclerosis.

Presentation of pathology

DR. ROSENTHAL At autopsy the external examination revealed a rather well built fairly nourished elderly man with marked cyanosis of the lips, nailbeds, and toes.

A 2+ pitting edema was present over the dorsum of both feet. The lower legs showed small varicose veins, marked stasis dermatitis with induration and scarring and an irregular ulcer over the right internal malleolus.

About 300 c.c. of clear straw-colored fluid was found in each pleural cavity and dense fibrous adhesions were present bilaterally. The lungs were heavy, markedly congested, edematous, and showed bullous emphysema mainly of the upper lobes.

As had been expected clinically, the main disease was in the heart and the aorta. The heart was moderately enlarged, mostly due to the hypertrophy of the left ventricle. It weighed 480 grams. Fairly dense fibrous adhesions were present between the visceral and parietal layers of the pericardium over both ventricles. The anterior half of the interventricular septum and the distal two-thirds of the anterior and lateral walls of the left ventricle were replaced by fibrous tissue. The posterior wall was involved only at the apex where the wall was very thin (4 mm.) and an organized mural thrombus was attached to the endocardial surface. At the base of the left posterior wall, near the septum, a 1.5 cm. ill-defined fresh infarct was present. Both coronary arteries were markedly sclerotic with narrow eccentric lumina. Old partially recanalized thrombus was found in the descending branch of the left coronary artery 2 cm. below its origin, and a fresh thrombus was present in the right coronary artery 6 cm. distal to its origin. These findings corresponded to the electrocardiographic changes and are mainly responsible for the death of this patient. The most interesting finding was encountered on examination of the aorta. Externally, the aorta showed no apparent distortion except for slight narrowing just below the origin of the left subclavian artery where a firm mass was felt. We had some difficulty in finding the lumen which was less than 5 mm. in diameter. The rest was obliterated by a red-brown dry and partially brittle thrombus. When the aorta was opened, it became immediately evident that there was a linear narrowing with a rigid, calcified diaphragm-like structure (1.5 cm. in width) protruding from it. The thrombus was firmly attached to it, which further narrowed the lumen



Fig. 3. Site of coarctation with vegetation.



Fig. 4. Fixed slide preparation of site of coarctation with vegetation.

At the coarctation the entire circumference measured 5 cm. The arch measured 9 cm. and the descending segment 7 cm. in circumference. Below the coarctation there was the characteristic jet lesion the localized intimal thickening. Atherosclerosis was present only in the abdominal segment. There was no anomaly of the main branches of the arch. The left subclavian artery was dilated and measured ? cm. in circumference (Figs. 3 to 6).

The rest of the organs showed marked acute and chronic congestion. A 3 cm. organizing infarct was found in the spleen.

Another finding of interest in this case was a typical megaesophagus (Fig. 7). The distal two thirds were markedly dilated and measured 8 cm. in diameter, while the

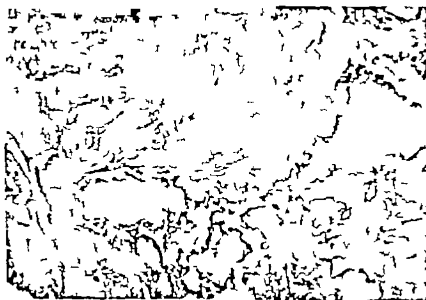


Fig. 5. Thrombotic vegetation. (× 125.)



Fig. 6. Heart. Fresh posterior wall infarct. (× 40.)



Fig. 7. Megaesophagus with cardial ulceration.

cardioesophageal junction was narrow with thick indurated wall and a large chronic active peptic ulcer. This finding explains very well his digestive disturbances which for many years, were considered to be psychosomatic. Most of his symptoms related to the vascular insufficiency were also thought to be hypochondriac in nature but the anatomic findings proved the existence of vastly different causes.

Final anatomical diagnoses: (1) Coarctation of the aorta with calcification and thrombotic vegetation (2) generalized arteriosclerosis (3) severe coronary sclerosis with old occlusion of the left coronary artery and fresh thrombosis of the right coronary artery (4) old anterolateral and septal myocardial infarct (5) mural thrombus of left apex (6) organizing infarct of spleen (7) chronic and acute congestion of viscera (8) bullous emphysema of lungs (9) megaesophagus with chronic active peptic ulcer of cardia (10) varicose veins and (11) stasis dermatitis with old scars and ulceration

Circulatory and respiratory changes in patients with Laennec's cirrhosis of the liver

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The hepatosplanchnic hemodynamic changes associated with cirrhosis of the liver are well known. They consist of a reduced total hepatic blood flow, portal hypertension, and the extensive formation of collateral venous system that bypasses the hepatic bed. The collateral vessels are perhaps, largely the consequence of portal hypertension. On the other hand, the cardiovascular and respiratory changes that occur in patients with cirrhosis of the liver have not received the same attention. In recent years special endeavor to elicit the hemodynamic accompaniment of cirrhosis of the liver has been made by a number of investigators. The purpose of this review is to outline in detail the observed circulatory and respiratory changes in cirrhosis of the liver and to discuss the probable mechanisms for their occurrence in severe liver disease.

Respiratory changes

The pulmonary ventilatory changes associated with cirrhosis of the liver were studied by Heinemann and associates and by us, (Table I). There are no consistent changes in mechanical ventilatory function or lung volumes[1] noted in patients with severe liver disease (Table I). The changes observed most often are related to nonhepatic disorders of the respiratory system. However, in the presence of severe ascites, the vital capacity may be reduced moderately. In the presence of obesity and marked ascites, compression of the lung volume also results in a decrease in the diameter of the airways and a degree of obstruction to airflow. Furthermore, all ventilatory capacity values are expected to be reduced in the presence of pulmonary congestion which may be associated with severe liver disease.

The most striking alterations in gas exchange which have been noted in virtually all patients with severe liver disease are hyperventilation with respiratory alkalosis[3] and hypoxia of variable proportions. Table II summarizes the gas exchange data from a group of patients with cirrhosis of the liver that was studied in our laboratory. This is representative of a number of studies previously reported.[2-] The degree of hyperventilation and respiratory alkalosis is roughly proportional to the severity of the liver disease but did not correlate with either the degree of arterial desaturation or the magnitude of venoarterial ad

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Table I. Ventilatory capacity studies in patients with cirrhosis of the liver

	FEV* (ml.)	FEV %† (%)	FVC (ml.)	FVC%‡ (%)	Ascites
1	2370	52	4600	108	None
2	1900	49	4000	99	None
3	2000	48	3655	89	+
4	1400	50	2800	62	None
5	1450	48	3000	80	++
6	1720	75	2270	70	None
7	2250	50	4490	112	None
8	2000	69	2900	85	None
Normal		67 ± 5.8		100 ± 11	

*FEV, 0.5 second forced expiratory volume; FVC, forced vital capacity; PVC, predicted vital capacity.

†FEV% = FEV × 100 / FVC

‡FVC% = FVC × 100 / PVC

Table II. Alveolar ventilation and gas exchange in patients with cirrhosis of the liver

			SaO_2	$PaCO_2$
N	24	24	27	27
Range	2.89 – 9.16	5.52 – 13.5	80 – 96	18 – 40
Mean ± SD	5.56 ± 1.5	9.66 ± 2.3	91.6 ± 4.1	32.2 ± 5.2
Normal	4.44 ± 1.08	6.32 ± 1.5	>95	37 – 44

	PaO_2	A-a	pH	HCO_3	Base excess
N	26	26	25	24	24
Range	45 – 89	23 – 72	7.35 – 7.50	12.5 – 28	−11 to +5
Mean ± SD	71.3 ± 12.6	43 ± 13	7.44 ± 0.04	21.3	−2.4
Normal	>85	13 ± 6	7.37 – 7.43	23 – 27	−2 to +4

V_A, alveolar ventilation (L./min.); V_E, minute ventilation (L./min.); SaO_2, systemic arterial O_2 saturation (%); PaO_2 and $PaCO_2$, O_2 and CO_2 tensions in the systemic arterial blood on room air breathing (mm. Hg); A-a, alveolar-arterial O_2 tension gradient on room air breathing (mm. Hg); pH, arterial [illegible]; (base excess in mEq./L.); HCO_3, plasma bicarbonate.

mixture. The observed alveolar ventilation represented 58 ± 10 per cent of the total minute ventilation and it was significantly lower than the predicted ratio of 70 per cent, indicating that the physiological dead space is increased in patients with cirrhosis of the liver. The V_A/V_E tended to decrease with increased ascites (Fig. 1) which was largely the result of increased dead space ventilation. This is particularly significant in the light of the expected change with ascites being a decrease in V_D as noted in obesity where V_E tends to decrease with increased obesity instead of an increase as noted here. Hyperventilation was present at all levels of consciousness and persists apparently unrelated to the presence of anemia, fever, pulmonary disease, or hypoxia.

The mechanism of hyperventilation seen

V/Q (PER CENT) plotted against ASCITES: NONE, MODERATE, MARKED (y-axis 30–80)

Fig. 1. Relation between the ratio VA/Q and the degree of ascites in patients with Laennec cirrhosis of the liver.

in cirrhosis of the liver remains obscure. Certain factors, singly or combined, have been assumed to stimulate the respiratory center and to perpetuate the respiratory drive. In the unanesthetized dog the infusion of nonacidifying ammonium salt increased respiratory drive and led to respiratory alkalosis. Hyperventilation with respiratory alkalosis, in turn, has been observed to increase the blood ammonia concentration and to enhance the ammonia toxicity through impairment of oxygen utilization at the tissue level. Whether this increase in blood ammonia level of hyperventilation is solely the result of an increased muscular activity remains to be seen.[1] However, the poor correlation between the circulating level of blood ammonia and the level of ventilation casts some doubt on the role of ammonia. It was suggested that the ratio of the diffusible to nondiffusible ions determine the magnitude of the respiratory drive rather than the absolute value of the ammonia blood level.[13] While the role of ammonia in the respiratory drive remains unclear, other primary amines[13] of intestinal origin also have been implicated. These compounds reached the systemic circulation by the 2 types of shunts described below.

The decreased arterial oxygen tension, that is due predominantly to venoarterial shunting, may play an additive role in the respiratory drive that is associated with cirrhosis of the liver. However, with the exception of a few patients, the arterial oxygen tension is not sufficiently low to be the singular cause for this increased ventilation. Furthermore, there is a poor correlation between the observed systemic arterial oxygen tension and minute ventilation which suggests again that additional or independent factors are responsible for the increased respiratory drive.[14] Such a conclusion is further substantiated by the observation that the breathing of pure oxygen for 30 minutes failed to decrease alveolar ventilation. The arterial CO_2 tension in 24 patients with cirrhosis of the liver was 32 ± 5 mm. Hg on breathing of room air and 31 ± 4 mm. Hg on breathing of 100 per cent oxygen.

It is interesting to note that in our studies (Table II) the mean plasma bicarbonate is low 21.3 mEq./L. and the base deficit is slightly increased (base excess = −2.4 ranging as low as −11). Moreover, we were able to calculate from the data of Vanamee and associates[2] whose patients had more severe liver disease and more severe hyperventilation that the base deficit was greater. The average was −4.1 in patients without coma and −5.1 in patients in coma. A decrease in blood buffer base would tend to increase the sensitivity of both the peripheral and central chemoreceptors to hydrogen-ion (H+) stimuli. The decrease in plasma bicarbonate presumably would indicate a decrease in cerebral spinal fluid (CSF) bicarbonate which is likely to be accompanied by a lower CSF pH (normally 7.32 at blood pH 7.4). Under these circumstances, hyperventilation would tend to be maintained since any reduction in ventilation with a subsequent rise in CO_2 tension will raise CSF H+ concentration and stimulate breathing. This would tend to prevent the expected decrease in ventilation when the patient is placed on 100 per cent oxygen breathing if one assumes that the hypoxia were a factor in the sustained hyperventilation. This, apparently, is the reason our patients showed no decrease in ventilation on 100 per cent O_2 breathing in spite of the fact that in some instances the PaO_2 was as low as 45 mm. Hg. The

use of the sustained low bicarbonate is not clear, but it is known to occur in chronic hyperventilation in subjects that experience altitude hypoxia and in persons who are subjected to prolonged hyperventilation by mechanical ventilation.

Thus the primary cause of hyperventilation remains obscure, but certainly the possibility of an interdependence of multiple factors which include increased circulating metabolites and hypoxia in the presence of a reduced bicarbonate in the blood and spinal fluid seems to offer the best possibility of an explanation of the sustained hyperventilation.

Circulatory changes

Mechanism of peripheral arterial desaturation. Peripheral arterial desaturation of oxyhemoglobin is frequently encountered in patients with advanced cirrhosis of the liver. The degree of hypoxemia is usually mild, but in some instances, marked peripheral cyanosis, associated with clubbing of the digits, is observed. This has been a clinical entity with obscure mechanism. It was first recognized by Fluckiger in 1884 in a woman with no evidence of cardiorespiratory dysfunction.[7] Subsequently similar observations were reported in both children and adults.[8-20]

Snell[9] reported the presence of systemic arterial desaturation and observed a close relationship between the acuteness and the severity of the liver disease and the degree of arterial desaturation. He postulated that an abnormality of the red blood cell (hemoglobin) could be responsible for the observed hypoxemia. Later, Keys and Snell[21] ascribed the cause of the hypoxemia to a shift in the oxyhemoglobin dissociation to the right. Their finding of altered hemoglobin dissociation, which was denied by subsequent investigators,[4] was recently confirmed.[22] The magnitude of this displacement was consistent but small and it would neither explain the described large alveolar-arterial O_2 tension (A-a) gradient (Table III) nor the marked degree of arterial desaturation that was observed in some patients with advanced disease of the liver.[23] These observations could, however, be best explained on altered exchange of pulmonary gases.

In the patient with chronic alcoholism impaired diffusion might be conceivable as the result of a recurrent pulmonary infection with subsequent interstitial pulmonary fibrosis. The demonstration of a decrease in the A-a gradient on low oxygen air mixture suggested that this mechanism played no significant role in the observed hypoxemia of cirrhosis of the liver.[23] Whereas the finding of a large A-a gradient on 100 per cent O_2 breathing suggested the existence of a venoarterial admixture.[24,25]

In cirrhosis of the liver, 2 sites of venoarterial admixture (shunting) were described both anatomically[27,28] and physiologically.[16,23,24] The portopulmonary pathway, the consequence of portal hypertension, diverted the portal venous blood into the pulmonary vein via the periesophageal and mediastinal veins. Theoretically, it is not possible for these shunts to carry the calculated amount of blood that bypasses the alveoli[24] or to produce marked arterial oxygen desaturation owing to the high oxygen content of the portal venous blood.[21] These theoretical considerations coupled with the finding of an estimated blood flow through this pathway (averaged 45 ml. per minute per square meter)[22] pointed

Table III. Alveolar—arterial (A-a) O tension gradients (mm. Hg) in patients with cirrhosis of the liver (room air breathing)

	No.	Mean	Normal values
Abelman and associates[16]	5	35 ± 4.3	9.7 ± 4.3
Rodman and associates[24]	18	32.6 ± 11.2	0 – 15
Heinemann and associates	10	31.2 ± 9.3	0 – 15
Bashour and associates[23]	15	43 ± 16	13 ± 6

to the second possible site pulmonary arterioles-to-venules. The existence of this pulmonary site was further substantiated by demonstrating that mild to moderate exercise increased the degree of venoarterial admixture.[24] Furthermore the finding of a significant positive correlation between the extra hepatic shunted blood and portal venous pressure (judged from hepatic wedge pressure) suggested that the portal hypertension played an important causative role in the development of the portopulmonary pathway.[21] In this respect the failure to decrease the magnitude of the venoarterial admixture upon surgical anastomosis of the portal vein to the inferior vena cava would indicate that the pulmonary arterioles-venules shunts are responsible for the venoarterial admixture. The finding of a normal arterial O_2 saturation and A-a gradient on 100 per cent O_2 breathing in a woman who bled on several occasions from esophageal varices due to extrahepatic portal hypertension (Fig. 2) gave further support to the pulmonary site of venoarterial admixture (Table IV Case 1). A recent attempt to demonstrate anatomically in 13 patients with liver cirrhosis, these pulmonary arteriovenous anastomoses was made by injecting the pulmonary artery with a micro-opaque gelatin suspension. Instead Berthelot and coworkers[25] found marked arterial dilatation of the fine peripheral branches of the pulmonary artery within the lung parenchyma (in the alveolar wall) and on the pleura. These later resembled the cutaneous spider nevi. Pulmonary arteriovenous anastomosis did exist in one patient who was 65 years of age. In the light of the above physiologic findings, it would seem difficult to explain the hypoxemia observed in patients with cirrhosis of the liver on the basis of an incomplete equilibrium between gas in the alveoli and blood in the dilated and multiple capillaries in the alveolar wall and the dilated pulmonary arterioles, since the low PaO_2 on 100 per cent oxygen breathing would tend to exclude this possibility. Further studies should prove rewarding.

Clubbing of the digits. The cause of digital

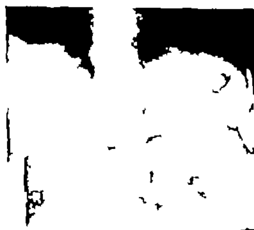


Fig. 2. Patient (Case 1 in Table IV) with extrahepatic obstruction of the portal vein which was demonstrated by the splenogram and later proved surgically.

Table IV. Pulmonary and peripheral gaseous exchange in extrahepatic portal obstruction (Case 1) and in Laennec's cirrhosis of the liver (Case 2)

	SaO_2	Peripheral AVo_2		A-a gradient (mm Hg)	
	(%)	(%)	mm Hg	Room air	100% O_2
Case 1	95	26	76	5	69
Case 2	89	4	8	64	577
Normal	>95	42 ± 13	49 ± 7	13 ± 6	48 ± 16

Peripheral AVo_2, arteriovenous O_2 difference across the hand, in per cent O_2 saturation (%) and in O_2 tension (mm Hg). A-a gradient, alveolar-arterial O_2 tension gradient on room air breathing and 30 minutes on 100% O_2 breathing. SaO_2, systemic arterial O_2 saturation (%).

clubbing occasionally associated with cirrhosis of the liver is not clear Clubbing of the digits from various causes was uniformly accompanied by a small peripheral (across the hand) arteriovenous O_2 and CO differences,[44] a decreased digital capillary blood flow [35] and digital oxygen consumption [36] which suggest the presence of blood shunting across the fingers from digital arterioles to venules through the existing arteriovenous anastomosis.[34,37-39]

Similar peripheral gaseous exchanges were noted in the patient with cirrhosis of the liver with marked palmar erythema.[34,40] This latter clinical finding shares the same pathogenesis and it is believed to precede clubbing of the digits in some patients with cirrhosis of the liver [41] In addition to the peripheral site of blood shunting an intrapulmonary right to-left blood shunting was also described [34] The disturbed circulations in both lung and peripheray are interrelated and after the resection of the primary lung lesion,[42,43] they returned to normal. A recent finding by Hall and Laidlaw[44] strongly indicated that reduced ferritin had bypassed the lungs and produced peripheral vasodilatation In cirrhosis of the liver the vasoactive substance whether it is a ferritin compound or not may gain access to the systemic circulation through either the intrahepatic shunts[illegible] and then through the pulmonary shunts or by the way of the portopulmonary shunts. The former is the larger therefore it would represent the most significant site.

Cardiac output and blood volumes A hyperkinetic state may be associated with disease of the liver The increased cardiac output results presumably from peripheral vasodilatation with increased peripheral blood flow [43,44] This is suggested by the frequent occurrence of warm hands, wide pulse pressure and capillary pulsations in these patients, and supported by the finding of an increased blood flow to the hand.[40] These circulatory changes at the periphery occurred independently of vascular changes in other vascular beds (splanchnic renal and cerebral) and in spite of an increased cardiac output the blood to these vascular beds may either be normal or diminished Again as in the presence of clubbing of the digits, a circulating vasoactive substance(s) is postulated to produce peripheral vasodilatation in patients with disease of the liver On the basis of the findings of 3 distinct circulatory patterns, Kontos and coworkers[40] suggested a number of factors (neurogenic, metabolic hypocapnea and even bradykinin) rather than a single cause to be responsible for the observed changes at the periphery as to whether the process of vasodilatation was limited to the skin to the muscle or to both.

Elevated cardiac indices have been observed clinically in the presence or absence of ascites and in patients with only fatty infiltration of the liver [43] Clubbing of the digits is usually associated with high cardiac output but this is not necessarily true for palmar erythema or spider nevi [44] This hyperkinetic state has been likened to that associated with beriberi Paget's disease and systemic arterio-venous fistula.[44] The generalized arteriolar vasodilatation may indeed be acting as multiple arteriovenous fistulae in parallel.[43]

The increase in total blood volume that is seen in cirrhosis of the liver is primarily the result of an increase in plasma volume with little or no change in red cell mass.[illegible] Using red cell labelled radioactive chromium Eisenberg[illegible] studied the relationship of the total blood volume and the presence of esophageal varices and/or peripheral cyanosis. He observed a significant increase in the plasma volume in patients with esophageal varices and of the red cell mass in patients with peripheral cyanosis in their absence, patients with cirrhosis of the liver had normal plasma volume and red cell mass. Thus, the hypervolemia of cirrhosis of the liver is related to the erythropoietic factor in the cyanotic patient and to the expanded capacity of the vascular bed in the presence of varices. This hypervolemia is reminiscent of that seen in clinical conditions associated with decreased peripheral resistance (i.e. pregnancy and systemic arteriovenous fistula)

Myocardial changes The increased cardiac output and total blood volume might conceivably lead to cardiac hypertrophy Indeed in the study of Lunseth and coworkers[illegible] and in our study (*Table V*) myocardial hypertrophy was frequently observed at postmortem examination of patients with Laennec's cirrhosis. In one

third of our patients, the heart weighed more than 400 grams. In 19 patients, the myocardial hypertrophy could not be explained by the known causes of heart disease. Thirteen of these 19 patients had varying degrees of myocardial fibrosis (Fig 3). In the remaining 6 patients, the increased heart weight was at least in part due to interstitial and or myocardial edema, which was previously reported in cirrhosis of the liver[14] and observed by us. These microscopic changes were limited



Fig 3 Diffuse myocardial fibrosis in patient with Laennec cirrhosis of the liver

Table V Cardiac findings in 100 consecutive autopsies on patients with Laennec's cirrhosis (1957 1963)

Age, 29 to 82 years (average 56)	
Sex, male 64 female 36	
Race, 75 Caucasians, 20 Negroes, 5 Latin Americans	
History of excessive intake of alcohol in 80	
Hearts weighing at least 400 grams in 33 patients	
Etiology of hypertrophy unexplained	19
Coronary atherosclerosis	5
Hypertension and valvular disease	7
Cor pulmonale	1
Metastatic tumor	1
Myocardial fibrosis seen in 20 hearts	
A. With unexplained hypertrophy	13
B. With myocardial infarction	5
C. With other causes	2
Endocardial thickening 2 cases both with unexplained hypertrophy	
Clinical and pathological evidence of heart failure (in the absence of known heart disease)	4

preferentially to the inner layer of the left ventricular wall.[15,16] This myocardial picture is similar to that described in alcoholic myocardiopathy which consisted of interstitial and myocardial edema fragmentation and atrophy of the myocardial fibers and varying degrees of fibrosis.[7] The difference between these 2 histological features would seem to be a quantitative one with alcoholic myocardiopathy representing a greater affection of the heart

In spite of the increased frequency of the degenerative changes, few instances of heart failure were reported.[17] In the majority of instances the heart was able to increase its cardiac output under moderate stress[11] with no evidence of a decrease in cardiac reserve. The cardiac response in patients with cirrhosis of the liver to submaximal or maximal exercise is yet to be assessed. It would be reasonable to assume that the development of heart failure would depend on both the magnitude of the hemodynamic changes and the severity of the degenerative process in the myocardium. In our study 4 patients had clinical evidence of heart failure 3 of them in the presence of an adequate blood hemoglobin level. All 4 of these patients had early evidence of heart failure which progressed gradually into pulmonary edema at post mortem all of them had extensive myocardial fibrosis.

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Appraisal and reappraisal of cardiac therapy

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The treatment of cardiogenic shock. Part I
The nature of cardiogenic shock

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Although there have been significant advances in the recognition and treatment of arrhythmias following acute myocardial infarction, the syndrome of cardiogenic shock has continued to present a most serious prognosis. Despite all of the therapy that is presently available, it is responsible for a major proportion of the deaths due to acute myocardial infarction. The precise frequency of shock following acute myocardial infarction has varied with different reports and different criteria for the definition of this syndrome, but most studies have shown an incidence of about 10 to 15 per cent of all patients who are hospitalized with acute myocardial infarction. This indicates that several hundred thousand patients in the United States alone die of this syndrome each year. It is reasonable to believe that improvements in therapy which produce even relatively small advantages may result in the saving of many lives. Therefore, continued assessment of the nature of this syndrome and its response to different modalities of therapy is important.

Despite its frequent occurrence, the precise sequential hemodynamic alterations which occur in shock due to myocardial infarction have not been clearly defined. The number of human beings who have been studied with detailed hemodynamic measurements has been relatively small. It is a difficult syndrome to produce experimentally.

Experimental myocardial infarction with shock

Completely satisfactory experimental models which consistently simulate the hemodynamic alterations occurring in human acute myocardial infarction with shock have not been developed. While ligation of a major coronary artery in a variety of experimental animals has produced well-defined acute myocardial infarction, sustained reduction of cardiac output and arterial pressure are not consistently produced. Generally, death from ventricular fibrillation ensues or there is survival with little hemodynamic change. The most widely employed and perhaps the most consistent, experimental technique to produce reduction of cardiac output and arterial pressure is that of Agress[1] or modifications thereof, in which plastic microspheres are injected into the coronary arteries, usually via the ascending aorta. This method, when it is applied to dogs, has produced in some of them sustained

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arterial hypotension lowered cardiac output histologic and gross diffuse myocardial infarction (usually subendocardial) and increase in serum glutamic oxaloacetic transaminase which simulate the changes that occur in acute myocardial infarction with shock in human beings.

Although significant decrease of cardiac output and arterial pressure has been produced the mechanism of the arterial hypotension is disputed. It is reasonable to relate the initiation of the arterial hypotension to an acute reduction of cardiac output. However in several instances, the normal response to such an acute fall of cardiac output (i.e. a compensatory rise of systemic vascular resistance) has not occurred in acute myocardial infarction with shock. In other instances, it has been noted that relatively slight rises of systemic vascular resistance are not proportional to the degree of reduction of cardiac output. One group has reported consistent significant elevation of systemic vascular resistance with this method in studies performed shortly after coronary embolization (possibly before a stable hemodynamic state has developed). The experimental evidence has indicated also that the arterial hypotension following acute myocardial infarction cannot be attributed solely to congestive heart failure. Either no rise or an inconstant rise of left ventricular diastolic pressure has been noted soon after coronary embolization when there is considerable hypotension although intracardiac pressures may be elevated several hours later. Even though heart failure may occur later in the course of shock following acute myocardial infarction, it does not appear to be essential for its production in all instances. In some open-chest animals, however left atrial pressure elevation has been noted shortly after constriction of a coronary artery.

The pathogenesis of the arterial hypotension following acute myocardial infarction may also be studied by determining the efficacy of methods of elevation of the low arterial pressure. Our own investigations have suggested that venous pooling is not the principal cause of aortic hypotension in experimental acute myocardial infarction with shock produced by coronary embolization. Shunting of large volumes of blood from the venous system to the aorta produced no rise of central aortic pressure. However when systemic vascular resistance was increased mechanically by abdominal aortic obstruction with a balloon catheter there was considerable rise of central aortic pressure.

Thus there is considerable indication from studies of experimental acute myocardial infarction with shock that factors regulating systemic vascular resistance may be important in the initiation or prolongation of profound hypotension that is associated with acute myocardial infarction despite the probable initiation of this syndrome by an acute fall of cardiac output. Several investigators have performed experiments pertinent to this problem. Perhaps, the most revealing have been those of Constantin[3] who demonstrated that sudden coronary arterial occlusion may produce peripheral vasodilatation which is attributable to reflex decrease in sympathetic activity to the peripheral vascular bed. The afferent path for this reflex, most probably is by way of the vagus nerve. Other experiments have indicated that left ventricular receptors may initiate peripheral vasodilatation. It is conceivable that these may be activated when an abnormal stretch or systolic expansion of the acutely infarcted ventricle occurs.

Studies of human beings

A review of the available literature concerning hemodynamic alterations in humans with acute myocardial infarction with shock prompts at least 2 main conclusions (1) Detailed hemodynamic studies of these patients have been unusually sparse when one considers the importance and frequency of the syndrome. (2) Specific hemodynamic derangements may vary considerably among different patients who may present similar clinical appearances.

When the mortality rate is being considered response to therapy hemodynamic alterations, and criteria for shock should be rigidly (and perhaps somewhat arbitrarily) defined. Mortality rates are lower when shock is loosely defined than when stricter criteria are used. If criteria are adopted which consist of systolic arterial pressure of 80 mm. Hg or less, not attributable to arrhythmias or temporary hypo-

tension related to medication accompanied by clinical signs of shock such as cool skin oliguria and alterations of the sensorium 72 patients from 9 different experimental groups have been carefully studied There have been several other patients in whom it could not be determined whether such criteria were met Still others with cardiogenic shock were grouped with patients with shock from other causes and it was not possible from the data presented to separate the cardiac patients from the others.

Analysis of the data obtained in the relatively small number of patients who were studied in detail is difficult because hemodynamic measurements have been obtained usually at a single point in time and at varying stages of the shock syndrome Therefore sequential alterations are poorly defined Even though there is, almost invariably a reduction of cardiac output the magnitude of this reduction is variable and in several instances, the cardiac output is only slightly reduced and in the same range as in patients with acute myocardial infarction who do not develop shock which suggests that factors other than reduction of cardiac output may contribute to the arterial hypotension and shock syndrome in certain patients.

Analysis of reported alterations of systemic vascular resistance supports the view that in many instances systemic vascular resistance fails to rise sufficiently to maintain arterial pressure as it usually does in individuals without acute myocardial infarction when there is an acute reduction of cardiac output. The statement by some investigators that shock is a uniform syndrome characterized by low cardiac output and severe vasoconstriction with greatly elevated systemic vascular resistance is not supported by the reported data. Just as many patients with acute myocardial infarction have had elevated as have had normal values for systemic vascular resistance. There is little evidence from these data, therefore that vasodilators are necessarily rational and preferred means of therapy in all patients with acute myocardial infarction with shock.

Measurements of venous or right atrial pressure have also shown considerable variation among patients with shock following acute myocardial infarction Many of them were within the normal range and others showed various degrees of elevation About one third of reported patients with acute myocardial infarction with shock have had normal venous or right atrial pressures which indicates that the arterial hypotension associated with acute myocardial infarction is not always explainable solely by severe congestive heart failure at least not as it is gauged by present conventional clinical measurements. Similarly blood volume and central blood volume have almost invariably been found normal Of course it is possible that left-sided intracardiac pressures may be abnormally elevated or that the left ventricular function curve is depressed in response to increasing work loads, even in the presence of normal right atrial pressure but unfortunately there are few published data concerning these important parameters in human beings. Nevertheless, as seen clinically shock and congestive heart failure may coexist the shock may result as a later complication of severe congestive heart failure or congestive heart failure may develop later in the course of shock The failure is possibly attributable to diminution of coronary perfusion pressure coronary flow and resultant deterioration of left ventricular function Although there is almost undoubtedly severe depression of myocardial function the patient may present solely with the clinical appearance of shock and never show signs or symptoms of congestive heart failure.

It is obvious from this discussion of the available facts concerning the mechanism of both experimental and clinical cardiogenic shock that its pathophysiology is complicated as must therefore, be its treatment. The intelligent management of this syndrome depends on careful analysis of the sequential hemodynamic events which produce it. Whereas laudable efforts have been made to unify' theories of shock from all causes and to assign a common hemodynamic pattern to all forms of shock regardless of cause attempts must be made to delineate features of cardiogenic shock and their attendant therapeutic implications which separate shock due to acute myocardial infarction from other forms. There is little scientific basis for and

perhaps considerable hazard in transferring experimental and clinical results in the treatment of other forms of shock to clinical acute myocardial infarction with shock. For example it can be readily appreciated that the patient with acute myocardial infarction with shock may tolerate poorly therapeutic measures which further lower an already reduced coronary perfusion pressure (and thus coronary flow) whereas such measures may not be harmful (or may even be beneficial) in shock unassociated with coronary disease or acute myocardial infarction. Similarly agents with significant chronotropic effects may be hazardous when used in a patient with an acutely ischemic left ventricle, which is more susceptible to significant arrhythmias, despite a desirable enhancement of myocardial contractile force. This potential danger is not as important in other forms of shock.

One of the most important problems in determining the genesis and appropriate therapy of shock due to acute myocardial infarction is to attempt to form uniform hemodynamic subgroups within the broad group of patients with cardiogenic shock, many of whom present the same clinical appearance, although they may have widely disparate hemodynamic alterations. It may be possible to separate groups which have a specific hemodynamic as opposed to a purely clinical manifestation and thus, may be expected to have a more predictable response to a specific type of therapeutic pharmacologic agent or means of mechanical circulatory support. Future advances in the therapy of cardiogenic shock can be expected to rely heavily on intense detailed and probably computerized measurements of sequential hemodynamic and metabolic alterations from the onset of the syndrome and its immediately preceding events to its progression to irreversible circulatory deterioration.

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A controlled trial of propranolol in acute myocardial infarction

The value of β-adrenergic blocking agents in the management of angina of effort has been demonstrated. Propranolol was reported by Snow to have a beneficial effect in the acute phase of myocardial infarction. It was postulated that the lower mortality found in cases treated with propranolol was due to both the antiarrhythmic and oxygen-sparing effects of this drug.

We describe here the results of a fully controlled trial of the effects of propranolol on the mortality in cases of acute myocardial infarction.

All of the patients who were admitted to the King's College Hospital Group (London) and who were suspected of having had an acute myocardial infarct within the previous 24 hours were admitted to the trial, except those who had complete heart block or who were unconscious and were not able to take oral medication.

The diagnostic criteria that were used were pathologic Q waves with ST-segment elevation and later inversion of the T wave or suggestive changes of the ST segment and T wave or bundle-branch block on the electrocardiogram (ECG) accompanied by a significant and transient elevation of the serum glutamic oxaloacetic transaminase (SGOT) or serum lactic dehydrogenase (LDH). Necropsy proof of recent infarction was required if the patient died before these criteria were satisfied. Random allocation was employed and the trial was carried out double blind. Severity of infarct was estimated according to the prognostic index of Peel. The oral dose of propranolol was 20 mg. every six hours. Anticoagulants were given unless contraindicated and other medication was avoided; analgesics, digitalis, diuretics, and vasopressors were given as necessary. All patients had frequent 12-lead ECGs during the first 72 hours and 50 of the last 75 patients underwent continuous ECG monitoring for at least 48 hours.

Of the 155 patients admitted to the trial, 114 satisfied our criteria. Their ages ranged from 39 to 82 years (average 59.8); 79 were men and 35 women. Fifty-six patients received propranolol and 58 did not. The age distribution and sex ratio were similar in both groups. There were no significant differences between the distribution of coronary prognostic index scores in the 2 groups nor in the time interval from the onset of pain and admission to hospital nor in the time interval from the onset of pain and entry into the trial. This is important as it has been pointed out that the mortality rate in acute myocardial infarction falls steeply in the first 48 hours. This fact is not taken into account by Peel's prognostic index. Five patients with proved recent myocardial infarcts were withdrawn from the trial and 6 patients were not admitted.

Altogether 27 patients died, 14 (24.1 per cent) in the control group and 13 (23.2 per cent) in the treated group; clearly there is no significant difference. The patients withdrawn from or not included in the trial account for the reduction in mortality rate from the figure of 30 per cent found in this hospital in the previous year. Snow did not use either random allocation or double-blind administration in his trial and we feel this explains the discrepancy between his results and ours.

Table I shows the incidences of heart failure, shock, hypotension, and hypotension with sinus bradycardia, both over-all and developing for the first time in 24 hours in the trial. Heart failure is a well-known complication of β-adrenergic blockade and is thought to be due to decreased myocardial contractility. There was no difference in its over-all occurrence in this trial, and two deaths were attributed to it in each group. Eleven patients in the treated group and 5 in the control group developed heart failure for the first time after 24 hours. This difference falls short of statistical significance, but in the light of previous experience indicates caution in the use of propranolol in acute myocardial infarction.

Shock was present in the same number of patients in each group. Hypotension, however, with or without the other features of the shock syndrome, was more frequent in the treated group. The difference between the groups was statistically significant when the development of hypotension for the first time after 24 hours in the trial was considered. This reflects the known hypotensive action of propranolol which has found some therapeutic application.

Snow's suggestion, that the favorable effect on mortality that he observed might be due to the suppression of potentially fatal arrhythmias, was supported by a report that propranolol can abolish arrhythmias and transiently reduce ECG evidence of injury in experimental infarcts in dogs. We detected arrhythmias in 90 per cent of our patients, a figure comparable with those of other workers who use a constant monitoring system. Sinus bradycardia, a well-recognized feature of β-adrenergic

Table I Incidence of heart failure, shock, hypotension, and hypotension with sinus bradycardia

Complication	Total	Treated group		Control group	
		Total	After 24 hr	Total	After 24 h
Heart failure	63	30	11 (37)	33	5 (30)
Shock	28	14	7 (49)	14	7 (51)
Hypotension	51	29	21 (48)	22	13 (49)
Hypotension with sinus bradycardia	25	17	15 (54)	8	5 (55)

*The figures in parentheses denote the number of patients who were at risk with respect to the complication developing for the first time after 24 hours.

blockade, developed significantly more frequently after 12 hours in the treated group. Sinus bradycardia associated with hypotension also developed more frequently after 12 hours in the treated group. This was again statistically significant and is not an unexpected effect of β-adrenergic blockade. The number of patients who had other arrhythmias for the first time after 12 hours was comparable in the two groups. Thus our findings do not support the contention that propranolol reduces the number of deaths in myocardial infarction by suppressing arrhythmias.

The effect of propranolol on coronary blood flow and myocardial metabolism in myocardial infarction is not known. Work on animals and patients with angina pectoris throws some light on this problem. Intravenous propranolol in anesthetized dogs has been shown to reduce myocardial blood flow, to increase the resistance to flow, and to reduce the dilator response to nitrites.[11,12] Propranolol dilates neither the normal nor the atherosclerotic coronary vessels.[14] In patients with angina pectoris, propranolol reduces coronary flow and decreases consumption of myocardial oxygen in spite of increased oxygen extraction.[15] Thus, the well-established beneficial effect of propranolol in some patients with angina pectoris[1-10] seems to be due to a reduction of myocardial metabolic requirements and not to an effect on coronary flow, which is in fact reduced. Whether this action will be apparent after frank infarction where the reduction in coronary flow is more critical remains to be determined. We suspect that the reduction in coronary flow which is likely to be produced by propranolol may counteract any beneficial effect on myocardial metabolic requirements.

Our results, and those of others,[26] together with available evidence on the mechanism of action of propranolol in ischemic heart disease, strongly suggest that there is no indication for the routine use of propranolol in acute myocardial infarction.

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Long term assessment of steroid treatment of idiopathic childhood nephrosis

Since 1950 when cortisone and corticotropin became available intensive study of their use in idiopathic nephrosis began on both sides of the Atlantic Ocean Tent tive short-term therapy was the usual pattern intended to simulate the stress of an acute infection which was sometimes followed by a temporary diuresis nd occasionally by recovery on ithdra al. Such diuresis occurred occasionally u predictably nd usually transiently A the content and duration of steroid dosage increased t became clear that steroid ithdrawal was not essential t provoke diuresis and indeed was undesirable Many atients of intensive prolonged treatment followed the i troduction of prednisolone and prednisone in 1955 but they began t crystallize l t long term intermittent therapy nd continuous short-term therapy Results ha e been confusing and understanding of the natural history of the disease is sine qua non of proper appreciation of th impact of steroid treatment on the ituation hich was previously obtained. Studies of Heymann nd Starzma Galan (1949), Barness and associates (1950),[18] Barnett and associates and Arneil,[20] tackled the problems of natural history

Any easonable form of intensi steroid therapy (usually complemented by a low-sodium l tak antibiotic cover or fluid restriction) produced diuresis in the great majority of children th idiopathic nephrosis, eliminated proteinuria in a lesser proportion and as ineffectual in small minority Since the production of diuresis in the majority as not d'fficult, the major problem during the period of 1955 to 1965 has been the voidance of teroid overdosage and the oidance of relapses in the responsi cases. The minority ho lacked sensitivity to steroid was usually treated by diuretics. Unfortunat ly such sophisticated techniques as percutaneous renal biopsy with light immunofluorescent, and electron microscopy differential protein clearances,[22 24] and beta-1-c globul estimations[25] were not ailable in 1955 Nevertheless long term assessment of prednisolone therapy in 1967 must be based on the 1955 to 1960 group that was diagnosed before such refinements were available.

I Glasgow Scotland survey of the 5-10 year results in 100 per cent of the hildren who presented ith idiopathic nephrosis has been completed recently by Arneil and Lam[26] The results of these studies may be summarized as follow

A total of 45 children with idiopathic nephrosis was admitted during the period of 1955 to 1960. All of the children with the exception of 1 child (who recovered pontaneously) received intensiv prednisolone or similar teroid therapy hich amounted to pproximately 1 3 Gm of prednisolone for period of not less than 6 eeks. After the intensive continuous therapy no subsequent intermittent continuous steroid, or antibiotic therapy was given to the asymptomatic patient. A total of 93 per cent of the patients responded to intensiv therapy with diuresis and reduction or elimination of proteinuria. Forty per cent of the children recovered from proteinuria and remained well ith no relapses up to 5 to 10 years later without an long-term intermittent steroid therapy This result trongly suggests that prolonged steroid and antibiotic treatment is u necessary undesirable and extravagant for 40 per cent of children ith idiopathic nephrosis.

A total of 53 per cent of the patients responded and then relapsed once or more sometimes th variable degrees of proteinuria bet een gross episodes. On the long-term basis it as found that of the 53 per cent 22 per cent had remained ell and free of proteinuria for not less than 5 years at survey 22 per cent had persisting relapses and/or proteinuria 5 to 10 years after onset and 9 per cent died Three hildren ere unresponsive t repeated courses of steroid treatment but of these t ere ll and free of proteinuria 5 to 10 years later This fact is ell orth recalling hen one studies labus

for immunosuppressant therapy as effective in steroid resistent cases!

The over-all figures that were obtained for this survey ere that 5 years after onset 91 per cent were alive, 69 per cent ere ell, and 9 per cent were dead. Very similar figures have been reported from Philadelphia with 85 per cent alive 66 per cent well, and 15 per cent dead after 5 years. Manifestly the figures for any group of children with idiopathic nephrosis (as compared t congenital or secondary nephrosis) will ary with the frequency distribution of each variant within the group. Classification by specialized microscopy complement state and differential protein clearances was impossible in this group but the cruder parameter of excessive initial erythrocyturia as noted in 17 children of the 45 and the morbidity (29 per cent) and mortality (17 per cent) rates ere much higher than in the group without hematuria (18 and 7 per cent respectively).

I 1961 Arneil[10] drew ttention t the fact that the improvement in the prognosis of idiopathic nephrosis could be related to the ailability of sulfonamides and ntibiotics nd this fact was again stressed by Saxena and Crawford.[16] It is calculated that if deaths from infection wer eliminated recovery rat of 70 per cent would be achieved without any credit to steroid therapy. Conversely it may be true that the long-term beneficial effects of steroid therapy are largely limited to diminishing the risk of infection by precipitating diuresis and reduction of proteinuria t an earlier dat than could have occurred naturally. Contrary t this persuasiv argument however t tal deaths from renal failure fter 5 ears amounted t only 9 per cent, which is 13 per cent less than one ould have predicted from the presteroid day. [11]

What lessons are to be learned? First, that 90 per cent of the children responded well t short intensive course and 40 per cent required no intermittent or any other steroid therapy for 5 t 10 years subsequently. Therefore, it ppears justifiable t give long-term intermittent steroid therapy and/or ntibiotic therapy t all steroid-sensitive nephrotics if 40 per cent in fact remain well ith no such treatment. It is suggested that children with steroid-responsive idiopathic nephrosis receive 6 eeks of steroid treatment. If nd hen relapse occurs, further course of steroid should then be given and prophylactic intermittent steroid therapy begun in the knowledge that of those who relapse once, t least 75per cent will relapse again.

With hindsight one would wish very much t know the results of differential protein clearance by the simple and eminently practical technique of Cameron and Blandford.[19] This appears to be the most promising way of predicting steroid sensitivity and outcome and may ell replace rather than complement routine percutaneous renal biopsy especially if beta-1-c globulin estimations are concurrently considered. With biopsy assumed, the exacting task of immunofluorescence may yield better prognostication and rationale of steroid insensitivity than the rather confused results of light and electron microscopy t date.

The problem of immunosuppressant therapy is luna t today. That tarting early in the course of the illness produces response in some cases is strongly reminiscent of the dark days before antibiotics and steroid changed the prognosis of idiopathic nephrosis. It is usual with a new untried treatment, for those with initial success to publish their findings and for others with inconclusive or depressing data to remain inarticulate. Recent papers by West and colleagues,[20] White and colleagues,[21] and Grupe and Heymann[22] have claimed good results on fairly small numbers of a mixed group on conditions. This has not been our impression or that of some other observers I iew of the well-authenticated tendency t unpredicted spontaneous recovery in the nephrotic syndrome (even if steroid resistant) nd particularly in the nephritis of anaphylactoid purpura, great caution is required in interpreting such results. Suspicion is ttached to deaths not ttributed to immunosuppressants and one must watch lest once again nephrotics on such drugs die of infection. It is to be hoped that following the comments of Barnett[23] large nd controlled international trial of immunosuppressants in childhood nephrotic syndrome will give conclusive results. It would be unfortunate if 16 years after the introduction of immunosuppressant therapy one knew as little of that as we do today of the optimal usage of steroid therapy.

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Collateral circulation shunting and revascularization

The present interest in occlusive vascular disease nd rev scularization of organs nd limbs renders t most important to ha e physiologic understand ing of the proper descriptiv terminology

When the circulation t living cells becomes impaired the therapeutic objectiv is t improv the irculation before it becomes critically insufficient nd death occurs The process of providing circula tion adequat to prevent the death of tissue should be termed *revascularization* On the other hand hen functional obstruction to flow exists blood must seek lternate routes in order to reach mor distant area the phenomenon of detouring blood flow should be termed *collateral* circulation The well-known alternate pathw y of flow that develop in coarctation of the aorta, portal obstruction pulmonary arterial atresia, ligation of the inferior vena cava, etc are thus properly considered collateral circulation. I these instances, vessels hich are normally present become larger i luminal diameter so that they then conduct larger vol mes of blood around the point of obstruction hether it be arterial or venous. *Shunting* is term hich indicates a direct flow of blood through relatively large channels from one large vessel to nother It can be normal physiologic vscular phenomenon or it can develop only in the presence of peripheral scular disease A V aneurysms in limbs, artifical surgical hunts, nd congenital shunts (cirsoid aneurysms) re examples of large ascular sh nts.

These concepts of terminology re extremely im portant in clinical medicine. When tissue suffers from impairment of blood supply the cell must receive more blood or they ill f nction poorly or even die Therefore, to be effective therapy must provide an adequate blood supply to the cells themselves. This means there must be an adequate circulation in the minutest of blood vessels, the capillaries. T show clinically that the capillary circulation is adequate within an organ is possible today only by certain indirect proced res. Clinical bedside meth ods are frequently satisfactory nd practical For example the electrocardiogram can help in detecting myocardial ischemia. Angiograms are also usef l but they provide information regarding the large vessels only Angiograms do not measure the volume or rat of blood flow nor do they indicat what the cells are actually receiving They reveal only the vessels that are filled with the contrast material and only those hich are large enough to be seen grossly These large vessels, however often may be functioning either as collaterals or as shu t channels. A *cluster* of shu ts or collaterals may produce very vascular ppearance on the x-ray film but only by means of more precise measurements can the linician know whether the cells in the diseased area are actually receiving an adequate amount of blood to maintain lif nd necessary function. More than conventional angiograms are required to determine hether there is sufficient organic arterial disease t impair cellular function or whether sufficient collat eral essel ha e developed t provide adequat blood flow to the tissue.

Caution should be exercised in interpreting coronary angiograms which propose to demonstrate im proved coronary circulation as result of specific therapy The existence of many large arteries engorged with contrast material does not necessaril

mean that the myocardial fibers are receiving sufficient amount of blood. It must be shown that the blood is reaching the capillaries of the myocardium in adequate quantities. The above should not be construed to indicate that coronary angiograms and arteriography are not useful and sometimes necessary clinical tools. One should be cautious in their interpretation, however since large vessels filled with contrast material and presenting ery vascular appearance may in fact be functioning as collateral or shunt channels. I this case there is little or no information provided as to whether revascularization t the capillary level has occurred.

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Confirmation by autopsy for vectorcardiographic diagnosis of myocardial infarction*

I recent cooperative study of the diagnostic accuracy of the ectorcardiogram (VCG) and electrocardiogram (ECG) by 10 experienced vectorcardiographers, the recognition of presence of myocardial infarction (61.4 per cent correct diagnoses for the VCG and 62.1 per cent for the ECG) as far better than its localization (44 per cent correct localization for the VCG 49.2 per cent for the ECG). I addition, there were 16.6 and 16.4 per cent partially correct diagnoses of recognition of infarction for the VCG and ECG respectively. Partially correct means diagnosis of conditions in addition to myocardial infarction which were not present. The selection of the 28 cases ith old myocardial infarction was based on independent evidence which included 5 autopsies.

W were are that there was no definite independent proof for the correct localization of myocardial infarction in the majority of cases thout utopsy confirmation but the results showed least, much greater discrepancies among the observers in the localization of infarct than in recognition, and in this respect there was no essential difference bet een the cases with and without autopsy.

The opinion is quit common that the VCG permits better localization of myocardial infarction (MI) than the ECG. The result of less than 50 per cent correct localization in our study is, therefore, disappointing. Obviously localization of MI must be based on opsy correlation and w ondered if the presently vailable material of autopsy supported VCG localization of myocardial infarction (MI) can be considered as adequate.

A thorough analysis of ailable VCG literature on MI was made for different types of lead systems. Of 18 tudies ith the Frank lead system, autopsy material was available only in 6 in estigations. In 2 commu nica ions, the selection was based on the ECG only hich is of course, not an independent method. Only in the studies of Hugenholtz and associates[4] and Gunnar and associates, was the localization based on autopsy alone. I the 1 tudies without autopsy evidence, the localization could be made, of course only by ECG or VCG. The main emphasis was on clinical data which included the ECG even in most studies with autopsy material. The total number of MI cases for the Frank lead system that was reported in the vailable VCG literature, is 1,418 w th 177 autopsied cases. These cases are distributed among t least 5 different localizations, so that, for any given localization, the autopsy material is quite small. Furthermore, there is some duplication in the number of autopsies because the most recent publication of the same authors, with the largest number of cases, also incorporates some cases that were published earlier.

Thirteen investigations were performed with cube systems. The autopsy material in the study of Wolff and co-workers, which uses his double cube system, is the largest ailable and autopsy evidence as used for selection as well as localization. The percentage of cases in which autopsy was performed for the double cube system is, therefore, higher than that for any other lead system. The other investigations are similar to those performed with the Frank lead system, both in regard to selection and localization. The total number of 629 cases with 172 autopsies are distributed among differen MI localizations nd different lead systems (Grishman-Scherlis, Duchosal, Double Cube) so that the number of autopsies for y lead system and localization is small. There is also some duplication of material in the 3 studies of Wolff and associates with total of 128 utopsies.

Six investigations of Burch and associates wer collected by means of the Wilson-Burch tetrahedron lead system autopsy as used in the later communications of Burch and associates[4] for selection as ell as localization. The percentage of cases in which autopsy was performed is larger but the absolute umber is smaller than that accumulated with the Frank or cube systems because this lead system is

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used mainly by this group. Again, ther is considerable overlap of the number of autopsies in the arious communications which is hard t estimate.

The number of investigations with the F ank lead ystem exceeds that with other lead sy tems which reflects its increasing use. This is contrast with the relativ ely small number (12.5 per ent) of cases i wh h a topsy was performed. The topsy mat ral of MI hich has accumulated over the past 10 to 15 years is surprisingly small nd far from adequate to substantiate VCG localiz tion. An ac elerated program of stud is needed for the im mediate accumulation of utops material order t confirm VCG loc lization of M I. Perhaps this rgent task ould be developed on ooperati basis.

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PATHOLOGIC PHYSIOLOGY Mechanisms of Disease by William A. Sodeman and William A. Sodeman, J Philadelphia and London, 1967 W B Saunders Company 1051 pages Price $19

This book is in its fourth edition which attests to its usefulness and success The contributors are able men in their respectiv fields and most of them are clinicians who understand the mecha nisms of disease The fields of medicine that are eviewed are important nd epresent common problems in medicine The material has been brought up to date Unfortunately the precise mechanisms of disease are not known, but the espectiv contributors have summarized the present concepts Some problems are only briefly discussed for example the effect of pregnancy on the circulation (page 312) However it would be impossible n text of this size to exhausti all the problems in few discussions This is f irly good book hich is concerned with the most importa ver d ficult t explain, problems clinical medicine

PHYSIOLO OF MUSCULAR EXERCISE. American Heart Association Monograph, No. 15 P oceedings of Symposium held Feb 7-9 1966 in Dallas, Texas edited by Carleton B Chapma New York 1967 America Heart Association 236 pages Price $3

This book is an accumulation of paper presented t symposium on the physiology of muscular exercise The paper ha been published as supplement to Cir lation in March 1967 The persons ho are participating in the ymposium ha been devoting their major effort to the study of exercise The papers are good and this monogr ph continues the high tandards that er established by previous ones This is good monograph on exercise lthough as would be expected only selected aspect of the problems are presen ed

CARD AC SURGE Y Edited by Joh C Norman New York 1967 Appleton-Century-C ofts, 603 pages Price $15 00 cloth $9 75 paper

This book is compilation of articles by 56 con tributors The book fills in part ed in this important field. Up this time there has not been single volume hich embraces the field of cardiac su gery in significa t detail. The editor does not ha clinical experience of the subjects but he has show good judgment in his selection of on ributors, ho are acknowl-edged authorities in the subjects they cover Each chapter is written t present the point of view of the uthor nd should not be looked pon as the gospel

The first third of the book is devoted to general considerations of ph siology techniques of cardio-pulmonary bypass, monitoring and management of cardiac arrest. The second section is concerned th cardiac surgery in infants and children and the third section is concerned with cardiac sur gery in adults Complications are reviewed in separate section. A final section is given to transplantation, assisted circulation, cardiac prostheses, and the future of cardiac surgery Abunda t references are given at the end of each chapter This book should serv as an excellent introduction to the field of cardiac surgery as review of particular topics, and as source of ready referenc

SUPPORT OF THE FAILING CIRCULATION By John Hines Kennedy Springfield 1967 Charles C Thomas publisher 138 pages Price $7 50

This is short monograph on the concept and problems concerned ith the use of n artificial pump to support the circulation in heart failure or hen it is in need of rest There is really ery little in this monograph that is not alread know t those persons ho would be expected to use such pump Surely there is no pump et av lable for general use nor is their sufficient control data to support the alue of such pro-cedur in clinical practice The author devotes more than half of the 112 pages of his text to the clinical applications to yet not fully established procedure. He fails to define adequately the many problems unsol ed. Such discussion could stimulate interest to those in fields other than surgery and cardiology in an effort to try to solv the many problems It is doubtf l that this short monograph ill assist many eaders

FUNKTIONSDIAGNOSTIK DES GESUNDEN UND KRANKEN HERZENS, Beziehungen zwischen Herzgrosse und Leistung on Prof Dr H Reindell, Doz Dr K. Konig Doz Dr H Roskamm Stuttgart, 1967 Georg Thieme Verlag 794 pages

This book comes from the most active German enter for studies of the influence of activity on differen circulatory ariables Physical capacity has been determined on bicycle ergometer ith imultaneous and continuous recording to respira tion, heart rate, oxygen consumption, and other variables Heart size was determined on ray film and total blood olume wer used as

ve tatn for the dimension of the circulatory system and are related to the ability to perform physical exercise both in normal persons and in patients with different circulatory disorders. The influence of digitalis on the measured variables was studied and the results of surgical intervention in several types of congenital or valvular heart disease were assessed. One item that seems to have interested the authors particularly is the question of latent or manifest decompensation as well as what they call decompensation of old age. Many of the ideas put forward in this book are far from the physiology that American physicians are used to and much of what the authors emphasize is more an expression of what they believe than real fact. None the less, the book contains a large amount of interesting factual material which may be of value for physicians with a reading knowledge of German and an interest in exercise physiology in health and disease.

SURGERY FOR ACQUIRED CORONARY DISEASE. By William H. Sewell, M.D., F.A.C.S., F.A.C.C., F.A.C.C.P., F.I.C.A. Springfield, Ill., 1967, Charles C Thomas, Publisher. 377 pages. Price $18.50.

This monograph is by a surgeon who has devoted a considerable amount of his time to the subject discussed. He presents very well the surgical point of view for the management of coronary disease. Unfortunately, no control studies are presented to show the comparison between elegant medical and elegant surgical management of acquired coronary disease. The reviewer finds a failure of Dr. Sewell, as well as others who write on the subject, to acknowledge the extended pioneering work of Doctor Claude Beck. He was really the father of surgery of the management of ischemic heart disease. Dr. Sewell's book is well organized and illustrated. Those who wish to learn the present-day concepts on surgical management of ischemic heart disease will find the book very useful. They will not find well-controlled observations that evaluate the procedure, however. With continued improvements in cardiac surgery and with better selection of patients, it will be necessary to know more about surgery for coronary heart diseases.

Books received

CARDIAC STIMULANT SUBSTANCES, Vol. 6, Medicinal Chemistry, A Series of Monographs, by Roland H. Thorp and Leonard B. Cobbin. New York, 1967, Acad. Press, 288 pages. Price $12.00.

ON THE CONTROL OF LIPID FORMATION. By J. C. DeHaven and N. Z. Shapiro. New York, 1967, S. Karger A.G. 63 pages.

VECTORCARDIOGRAPHY. By Irwin Hoffman and Robert C. Taymor. Philadelphia, 1966, J. B. Lippincott Company. 428 pages. Price $20.00.

DAS KARZINOID: Klinik, Endokrinologie, pathologische Anatomie, Pathogenese und Therapie. By Hans Joachim Kahler. New York, 1967, Springer-Verlag Berlin. 281 pages. Price $19.30.

THE HISTORY AND GEOGRAPHY OF DISEASE. By Folk Henschen. New York, 1967, A Seymour Lawrence Book, Delacorte Press. 344 pages. Price $10.00.

MODERN TREATMENT, Vol. 4, No. 2, March, 1967. (1) Treatment of Shock, by Leslie A. Kuhn. (2) Treatment of Arterial Disorders of the Extremities. New York, 1967, Hoeber Medical Division, Harper and Row. 1,500 pages per year. Price $16.00 per year.

MODERN TREATMENT, Vol. 4, No. 3, May, 1967. (1) Treatment of Kidney Stones, by Felix O. Kolb. (2) Treatment of Acute Oral Ulcerations, by Edward A. Graykowski. New York, 1967, Hoeber Medical Division, *Harper and Row*. 1,500 pages. Price $16.00 per year.

TEORIA Y PRACTICA DE LA ELECTROCARDIOGRAFIA. By *Enrique* Cabrera and Alfonso Gaxiola, 2nd edition. Mexico, 1966, La Prensa Medica Mexicana, 324 pages.

CECIL-LOEB TEXTBOOK OF MEDICINE. By Paul B. Beeson and Walsh McDermott, 12th edition, Philadelphia, 1967, W. B. Saunders Co. 1,735 pages. Price $20.50.

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Editorial

Posttransfusion hepatitis

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As surgical experience in the correction of cardiac defects accumulates, the rate of surgical mortality declines and non operative causes of morbidity become increasingly significant. Since the patients who undergo heart surgery may receive large amounts of blood they run an appreciable risk of developing posttransfusion hepatitis (PTH) In addition to the major problem of acute and chronic liver failure diagnostic and therapeutic problems peculiar to such cardiac patients can be aggravated by hepatitis. The initial anorexia that is seen with hepatitis may be confused with digitalis intoxication and coagulation abnormalities are often accentuated in those patients who are placed on anticoagulant drugs. The significance of PTH warrants an examination of current problems in its epidemiology and control.

Etiology One of the perennial epidemiologic problems has been identification of an etiologic agent or agents. Volunteer studies showed differences between infectious hepatitis (IH) and homologous serum hepatitis (HSH) with regard to incubation period stool infectivity clinical picture, and lack of heterologous immunity These differences led early workers to the belief that 2 different agents, virus A and virus B were responsible.

Both the cyclic incidence of IH[1] and the failure to isolate an infective agent suggest that a closely related group of similarly fastidious agents is responsible. The distinction between virus A and virus B is further blurred by the fact that PTH has incubation periods which have a unimodal distribution and a mean between those of classic IH and HSH [2] On the other hand the wide range of incubation times and the varied clinical expression (perhaps, including the postperfusion syndrome[3]) have formed the basis for the speculation that PTH may be caused by many agents. Indeed a great number of different "candidate agents have been isolated over the years, although none of these has achieved the right to be called "hepatitis virus

Human volunteer studies which might have helped define the cause of hepatitis, were stopped in 1953 because of the mortality rate of this disease Recent work with nonhuman primates suggests that they may serve as susceptible hosts for further in vivo studies.

Incidence and mortality Another epidemologic problem is the lack of agreement on the carrier rate. The incidence of PTH varies with the method of case finding A review of hospital records indicated that, of each 10 000 units of whole blood trans-

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fused at least 6 caused the development of icteric PTH which required hospitalization.[7] In a prospective search for icteric PTH in recipients of whole blood the number of infective units was tenfold higher (approximately 90 per 10 000 units of blood transfused) and the risk was proportional to the amount of blood given. Two recent reports suggest that the incidence of hepatitis carriers as measured by resultant cases of anicteric hepatitis may be tenfold higher again ranging from 600 per 10 000 units in Japan to 870 per 10 000 units in Philadelphia.

Host factors also play a role in the development of hepatitis (1) in early volunteer studies, infective plasma rarely caused disease in more than half of those exposed (2) infective plasma from a single donor caused hepatitis with a great range of incubation periods, (3) the incidence of icteric hepatitis is much lower in children than in older patients[1] and (4) the mortality rate in serum hepatitis increases with advancing age.[12]

Despite variable host factors and differences in attack rates, the over-all case fatality in large series of icteric PTH was 12 per cent. A reasonable conclusion is that of 1 000 patients who receive 1 unit of blood approximately 100 patients will develop hepatitis, 10 will become jaundiced and one will die of this disease.

Prevention What can be done to decrease the risk of PTH? Careful selection of donors has not provided the answer to this problem. Some workers have advocated the exclusive use of volunteer donors[4] others feel that the risk of hepatitis after the transfusion of blood which is obtained from commercial donors (excluding prisoners) is no different from the risk with volunteer donors.[13] Indeed the study with the highest infectivity rate (8 7 per cent) used blood primarily from volunteer donors.

Another method of curtailing PTH would be a laboratory test to identify those units of blood containing infectious material. Standard H and L functional tests of the liver are inadequate for this purpose. The recently developed hepatitis-infectious mononucleosis (HIM) test identifies with some success those people with active hepatitis or infectious mononucleosis, but it is also positive in 4?[17] to 62 per cent[1] of normal donors. Nevertheless, the test is no indicator of immunity to all of the possible infectious agents of PTH recipients with a positive HIM test before transfusions of blood developed PTH with a frequency equal to those with a negative test. It is clearly impractical to exclude half of the available donors. Some better method is needed to distinguish between the donors who are merely exposed to some agents and donors capable of transmitting hepatitis.

Another approach to the hepatitis problem would be to treat the blood of donors by removing or inactivating the infective agent. The removal of the agent from the red blood cells might be accomplished by extensive washing although the followup has been incomplete no hepatitis has been noted after the transfusion of frozen cells which receive such washing. Unfortunately washed red cells cannot satisfy the most transfusion needs. The possibility exists that some chemical or physical treatment will either sterilize the blood prevent infection before the administration of the blood transfusion or prevent disease in exposed persons. Although such treatment is available for some viral diseases, no chemical that is nontoxic to both whole blood and its recipient has proved effective against the agent of PTH.

Immune prophylaxis The use of commercial gamma globulin i e immune serum globulin (human) to prevent or attenuate PTH has been extensively studied. A rationale for using this material is the fact that aged plasma from convalescent hepatitis patients or from probable hepatitis carriers protected volunteers against icterogenic material.[14] The active principle in this protective plasma could well have been antibody against the agent of PTH. One might expect that gamma globulin from such plasma could provide passive immunity against this agent.

The administration of gamma globulin has commonly been by the intramuscular route. Whereas intramuscular gamma globulin has been shown to be effective in attenuation of IH[15] conflicting results have been obtained in PTH. Mirick, Ward and McCollum were able to decrease the incidence of icteric (but not anicteric) hepatitis by the use of 10 ml of gamma globulin in the week after the blood trans-

fusion and 10 ml. one month later. With another schedule, 10 ml. the week before transfusion and 10 ml. one month later no decrease in icteric PTH was seen.[3]

The above results may be contrasted with a study at this institution: patients who were to undergo open-heart surgery were given 10 ml. of gamma globulin intramuscularly at the time of surgery and 10 ml. one month later. No protective effect was seen,[27] although the gamma globulin reached a plasma peak 24 hours after injection. Re-evaluation of the protective effect of intramuscular gamma globulin given at various times before or after transfusion is presently underway in other centers.

Some workers have added gamma globulin to the blood of donors in an attempt to neutralize the hepatitis agent before transfusion. Whole immune serum globulin (human) has not been used in this manner because of the reports of serious side effects with the intravenous administration of this product, especially in hypogammaglobulinemic patients. These reactions have been related to anticomplementary activity associated with aggregated IgG immunoglobulin in commercial preparations.[28] Most workers feel that unmodified IgG should not be given by this route although no reactions were noted in a group of febrile patients with leukemia, who were given whole gamma globulin intravenously.[29]

In order to prevent clinical reactions to intravenous gamma globulin some investigators have further modified the globulin preparations that are obtained by ethanol fractionation. A pepsin-treated IgG has not caused reactions.[30] Although the decreased molecular size of this product leads to rapid excretion and a shortened in vivo half life, the antibody may be active. Creutzfeld and associates[31] have added enzymatically altered IgG to whole blood before transfusion and have reported a protective effect against both icteric and anicteric PTH. Another product, which has not caused reactions when it was given intravenously, is IgG modified by exposure to low pH.[32] The ability of this latter product to prevent hepatitis when it is added to whole blood is being studied on a large scale.[33]

Most commercial preparations of unmodified gamma globulin undergo continuing degradation during storage.[27] This degradation destroys anticomplementary activity but may also destroy specific antibody. Several methods of reducing breakdown of gamma globulin during storage are currently under evaluation.

The variability in results that are obtained with the use of different preparations of gamma globulin (with different times and routes of administration) deserves comment. Sahiar and Schwartz[34] have demonstrated feedback inhibition of IgM immunoglobulin with the administration of specific IgG in rabbits. Specific IgG has been given for prophylaxis of Rh hemolytic disease of the newborn. Rh-negative mothers, who have been given a highly concentrated IgG preparation of anti-Rh after the delivery of an Rh-positive infant, have not become actively immunized to Rh. It is interesting to note that the administration of saline active (presumably IgM) anti-Rh enhanced immunization to Rh-positive red cells in male volunteers.[35] Although several alternative explanations for these findings have been proposed, they may represent an extension of Sahiar and Schwartz's work to man. Attenuation of PTH by immune globulins may well depend upon the type of antibody and timing of antibody administration. The administration of specific IgG at the wrong time might damage the immune response to the agent of PTH. Improved active immunity against the agent of PTH might be obtained with the administration of pooled IgM if this were available.

If the severity of the disease is related to the number of infective particles that are administered, there is evidence from other systems that an addition of specific IgG to the blood before a transfusion may be helpful in amelioration, if not in the eradication of PTH. Viral agents can remain infective when coated with antibody.[36] Although infective titers of herpes simplex virus were reduced 100 fold by incubation of the virus with anti-viral IgG of rabbits, some particles remained infective in the presence of excess antibody. When anti-rabbit IgG of goats was added, the infectivity was further reduced an additional 100 fold. This work suggests that for immune elimination of the agent of PTH from the blood of donors, not only antibody but also antiantibody may be needed. The use

of IgG plus anti IgG in man for this purpose is a theoretically enticing but presently impractical proposition

Conclusions

Many measures have been proposed for the control of PTH and most of them have already been found wanting Studies of the use of immune globulins for amelioration or prevention of the disease have had conflicting results. Slight variations in the time of administration may have been critical The place of immune globulins in the management of this disease remains unclear

Since the risk of PTH is proportional to the amount of blood transfused one reliable method of reducing the incidence of the disease is the reduction of blood usage This has been appreciated by surgeons who have begun to use oxygenators with smaller priming volumes. Complete elimination of PTH must await identification of its cause

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Clinical communications

The straight thoracic spine in cardiac diagnosis

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Asymptomatic compression of the heart and great vessels by a chest deformity characterized by absence of normal thoracic kyphosis has been designated as the straight back syndrome. This deformity as described by Rawlings[1] in 1960 simulates organic heart disease by causing systolic murmurs, alterations of heart sounds, and an apparent enlargement of the cardiac silhouette. The clinical and hemodynamic features of this deformity have been described[2-4] in patients with normal hearts and the findings have been attributed to a relative decrease in anteroposterior chest dimensions. Similar cardiac findings are known to occur with other causes of chest narrowing such as pectus excavatum. The straight thoracic spine has not been reported in the presence of acquired organic heart disease or in children.

This is a study of patients with and without heart disease, some of whom also had straight thoracic spines. We have tried to determine whether or not the clinical findings are influenced by this deformity and have sought cases of "straight back syndrome" in the pediatric age group.

Materials and methods

A total of 504 consecutive patients were studied prospectively for evidence of skeletal deformities characterized by a lack of the normal thoracic curvature (dorsal kyposis)—the straight back. All were known to have heart murmurs and all were referred to Deborah Hospital as possible candidates for heart surgery. There were 250 patients with congenital heart disease (CHD), 200 with rheumatic heart disease (RHD), and 54 with innocent murmurs and no apparent heart disease.

The diagnosis of straight thoracic spine was made by inspecting the back with the patient in a standing or sitting position. The thoracic spine does not appear to have a curvature and the interscapular area has a deep "scooped out" appearance. The deformity is further demonstrated by examination of chest roentgenograms taken in the lateral and oblique projections (Fig. 1). Although there is a wide range in magnitude of normal thoracic curvatures, only those with no anteroposterior curvature below the level of the second thoracic vertebra were considered to be "straight." Changes in posture, attitude, or respiration did not significantly change this portion of the spine configuration. The degree of chest narrowing was expressed as a ratio of the anteroposterior dimension to the transthoracic dimension, a method similar to that of de Leon and

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Fig *1* Anteroposterior (*A*) lateral (*B*) right a terior oblique (*C*), and left anterior obliq (*D*) views of the chest showing a straight thoracic spine and narrowing of the cardiac space i patient ith no heart disease. The AP-transthoracic ratio is 34 per cent.

associates.[5] The height and weight of the children below the age of 13 years were plotted on the percentile charts of Stuart[6] to identify any correlation between chest narrowing and over all body build These charts allow the heights and weights of the individual children to be expressed as percentiles of the heights and weights which can be expected at a given age. A definite cardiac diagnosis was established by catheterization studies or by surgery for all of the patients in the CHD and RHD groups. In those with congenital lesions, the incidence of noncardiac anomalies was also recorded

Results

Congenital heart disease Of the 250 CHD patients, 23 (9 2 per cent) had straight thoracic spines (Table 1) Their ages ranged from 3 to 22 years with a mean age of 8 2 years there were no infants in the CHD group The cardiac lesions in these patients represented a variety of the more common congenital malformations. Nine of these patients had narrowing of the

Table I Congenital heart disease and straight thoracic spines

Patient No.	Age (yr)	Sex	Cardiac diagnosis	Height/weight percentiles	A P trans-thoracic (per cent)	A P chest narrowing	Other anomalies or defects
1	8	F	VSD PS*	35/<3	38	−	Myopia, prominent Harrison grooves, L chest prominence
2	11	F	VSD	60/80	41	−	—
3	17	M	CoAo	—	31	+	Mild pectus excavatum, short thumbs strabismus
4	7	F	VSD	10/<3	52	−	L. chest prominent strabismus
5	3	M	VSD PS	3/<3	48	−	Inguinal hernia mild pectus carinatum, supernumerary nipple
6	3	M	VSD PS, Rt Ao. Arch	35/15	50	−	—
7	4	F	VSD	85/50	25	+	Prominent Harrison grooves, L chest prominent
8	4	M	AS	75/15	40	−	Speech defect, cervical rib
9	4	F	PS	<3/<3	47	−	Prominent Harrison grooves
10	11	M	AR	35/20	36	+	L. chest prominent
11	5	M	VSD PDA	10/<3	46	−	Hypertelorism
12	5	M	PS	50/25	45	−	—
13	22	M	ASD	—	31	+	Mild pectus excavatum, short arms
14	9	M	PS	75/75	40	−	—
15	7	M	VSD	25/10	37	+	Fusion ribs 1 and 2 prominent Harrison's grooves, L chest bulge
16	15	F	AS	—	31	+	—
17	6	M	VSD Dextrocardia	30/45	45	−	R chest prominent, prominent Harrison's grooves
18	4	M	VSD	15/75	32	+	Pes planus supernumerary nipple, L chest prominent
19	6	F	PDA	65/65	40	−	—
20	9	M	PCAC	70/35	35	+	Inguinal hernia, L chest prominent
21	4	M	VSD PS Rt. Ao. Arch	75/50	50	−	Mental retardation, strabismus, L chest prominent
22	11	F	VSD	50/75	44	−	Severe myopia
23	14	F	PS	−	32	+	Thoracic scoliosis

Abbreviations VSD ventricular septal defect PS, pulmonary stenosis CoAo, coarctation of the aorta, AS, aortic stenosis AR, aortic regurgitation; PDA, patent ductus arteriosus; PCAC permanent common atrioventricular canal.

anteroposterior (AP) diameter of the chest with a pancaking effect on the heart, with encroachment anteriorly against the sternum and posteriorly against the spine. All of these patients had AP/transthoracic ratios of less than 38 per cent. The chest dimensions did not have a constant relationship to over-all body configuration some of the narrow chests occurred in patients who were not tall and thin (Patient 2 14 18, and 19) and some of the chests with the greatest anteroposterior diameter occurred in small underweight patient (Patient 4 5 and 9) In 73 per cent of the patients with straight spines, additional anomalies or defects were encountered which might be expected n any CHD group. Of particular interest are associated chest anomalies. There were six patients with a left chest prominence which may be acquired t is usually attributed to cardiomegaly and right ventricular hypertrophy Five patients had a prominent Harrison's grooves bilaterally Tw[illegible] tients (3 and 13) had a mild [illegible] [illegible]vatum which contributed to

narrowing. Two cases of anterior bowing (lordosis) of the thoracic spine were encountered and were not considered to be examples of straight thoracic spines. Patients 3 and 23 had the interesting combination of "straight" thoracic spine and a mild thoracic scoliosis—an apparent contradiction of terms.

None of these 23 patients had clinical, roentgenographic, or electrocardiographic changes which could not be explained adequately by the congenital cardiac lesion found in each patient. The straight thoracic spine did not interfere with the appropriate diagnosis in any case. There were no misleading heaves to suggest ventricular hypertrophy when none was present and there was no significant change in the intensity of murmurs with respiration. The only patient with fixed splitting of the second sound had an atrial septal defect. Only in Patient 22 was there an additional sign, an ejection systolic murmur (Grade III/VI) in the pulmonary area which decreased with inspiration. This patient had a small ventricular septal defect without pulmonary hypertension and the second heart sound was normal. In all other patients in the CHD group the straight thoracic spine was an incidental finding and did not contribute to diagnostic difficulties no matter how great the chest narrowing. Skeletal deformities and anomalies of many types were common (36.3 per cent) in the CHD group: scoliosis, pectus carinatum, pes planus, cervical or fused ribs, Harrison's grooves, and extra or short digits.

Rheumatic heart disease. Of the 200 patients in the RHD group, 4 (2 per cent) had clinical and x-ray evidence of straight thoracic spine (Table II). Three were studied preoperatively and one (Patient 4) was studied 2 years after open mitral commissurotomy. All of these patients had experienced varying degrees of congestive failure and none had the onset of symptoms prior to the age of 30 years. The shape of the spine had no apparent effect on accelerating or aggravating the clinical course. The degree of disability seemed compatible with the hemodynamic findings in each case. The two patients who had signs and symptoms of right heart failure had a prior history of several years of dyspnea and orthopnea. There was no knowledge of heart murmurs being detected during childhood in any of the patients and a diagnosis of "straight back syndrome" had not been made prior to this study.

The physical findings in Patients 1 to 3 were compatible with those expected with the indicated valvular lesions. The ejection systolic murmur in Patient 1 was attributed to pulmonary hypertension (the pulmonary artery systolic pressure was 66 mm. Hg) and did not vary with respiration. The systolic murmur in Patient 4 was characteristic of that described with the "straight back syndrome"; it showed a marked decrease with inspiration. This patient studied 2 years after commissurotomy was asymptomatic and had no residual signs of mitral stenosis except for a moderate increase in the intensity of the first heart sound.

The degree of chest narrowing in most of the patients was not great, 35 per cent in Patient 1 and within normal limits in

Table II. Rheumatic heart disease and straight thoracic spines

Patient No.	Age (yr.)	Sex	Cardiac diagnosis	Surgery	Systolic ejection murmur in pulm. area	AP/trans.
1	36	F	MR, pulm. hypertension	Mitral prosthesis	Grade III/VI (no respiratory variation)	0.35
2	44	F	MS	None	—	0.48
3	50	M	MR, AR, AS, pulm. hypertension	Mitral and aortic prosthesis	—	0.43
4	35	F	MS	Mitral commissurotomy	Grade III/VI (Grade I/VI with inspiration)	0.44

the other three. All four exhibited anteroposterior encroachment on the cardiac space as a result of cardiomegaly and the straight spine. Patients 1 and 2 in whom right ventricular angiocardiograms were done demonstrated narrowing of the right ventricular cavity with the chamber flattened against the sternum (Fig 2). There was no increase in right atrial pressure or clinical evidence of tricuspid lesions in any patient. Neither of the two patients with mitral regurgitation exhibited a ventricular knock,[7] which has been described as due to the diastolic impact of the left ventricle against the chest wall. Pulmonary valve closure was palpable in Patients 1 and 3 and its presence can be explained by the effects of pulmonary hypertension and mitral regurgitation. Fixed splitting of the second heart sound was not observed.

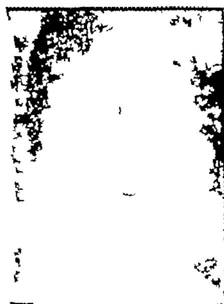


Fig 2. Angiocardiogram. Patient 3 of the RHD group. The right ventricular cavity is narrowed and vertically oriented and the pulmonary artery is dilated.

No heart disease. A total of 54 patients were examined because of the presence of heart murmurs and were diagnosed as having no heart disease; the murmurs were of the innocent variety. Of these, 38 were under 15 years of age. Four (Table III) of these were found to have straight thoracic spines and had the typical pulmonic ejection systolic murmur. These murmurs were Grade II–III/VI in intensity and disappeared or diminished with deep inspiration. One patient had wide splitting of the second heart sound with little respiratory variation (Fig 3). In this group there were 3 female patients and one male; the youngest was 11 years old and the oldest was 39. Three were tall and thin with narrow chests. Patient 4 also had mild pectus excavatum. Cardiac shunts and stenotic lesions were ruled out in 3 patients by catheterization studies, and angiocardiograms demonstrated flattening of the right ventricle and pulmonary artery against the anterior chest wall. There were no instances of straight spine without the clinical features of "straight back syndrome" as described by Rawlings[4] and others. All of these except Patient 1 were older than age 15. These 4 patients had been previously misdiagnosed as having organic heart disease (2 pulmonic stenosis, 1 atrial septal defect, and 1 ventricular septal defect). There were five other patients with innocent murmurs who had narrow chests with normal thoracic kyphosis and whose murmurs also diminished with inspiration. Apparently narrowing per se is a cause of innocent murmurs.

Table III. No heart disease and straight thoracic spines

Patient No.	Age (yr)	Sex	Ejection murmur	Catheterization	AP/Area	Tall thin body build
1	11	F	Grade III/VI	+	0 36	+
2	39	F	Grade III/VI	+	0 41	−
3	26	F	Grade II/VI	−	0 31	+
4	18	M	Grade III/VI	+	0 3	+

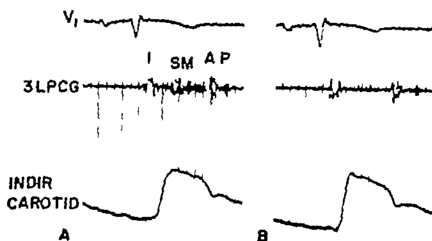


Fig. 3. Patient 2 of the group with straight back syndrome and no heart disease. There is a marked variation in the intensity of the murmur during expiration (A) and inspiration (B). The second heart sound is widely split during both phases of respiration. 3LPCG, third left intercostal space phonocardiogram.

Discussion

Compression of the heart is known to produce murmurs and changes in heart sounds which may lead to an erroneous diagnosis of heart disease. This compression may be due to pectus excavatum anteriorly or a straight spine posteriorly. Several cases of the latter have been described in detail in adults with no demonstrable heart disease. These cases of straight back syndrome are characterized by a systolic ejection murmur in the second and third left interspace which decreases in intensity with inspiration; frequently the heart sounds are altered and apparent cardiac enlargement by x-ray is caused by the pancaking effect of the anteroposterior narrowing. These findings are due to positional changes and compression of the heart with proximity to the sternum. The straight back syndrome has been noted with generous chest dimensions (7 patients of de Leon and associates) and one in this study have ratios of 41 per cent). In spite of these curious exceptions, most patients without heart disease exhibit a narrow chest associated with their straight spines. Examination of published cases as well as those reported here reveals that thoracic spine straightening does not usually involve the entire thoracic portion of the spine. The straightening as viewed from the lateral projection involves those vertebrae below the second thoracic and the entire retrocardiac portion. The spine is not a completely inflexible structure, though it does have well-defined curvatures, and the patients must be sitting upright or standing to appreciate the contour of the back. Straight thoracic spine is not always associated with the general appearance of good posture because stooping of the shoulders and forward angulation of the cervical spine also contribute to postural attitudes.

In the children surveyed in this study there was a wide range of A-P/transthoracic ratios and height/weight percentiles. Many of these proportions would be expected to change with continued growth and a tendency toward narrow A-P diameters in the teenage patients is noted.

The incidence of straight thoracic spine deformity may be estimated from those found in the acquired heart disease group, i.e., 4 cases in the RHD group of 200 or 2 per cent. The much higher incidence in the patients with congenital heart disease is not unexpected as congenital defects are likely to occur in clusters. The straight

spine in this group therefore is believed to represent one of several types of associated skeletal anomalies. Spitz[8] has found an incidence of 10 per cent in patients with atrial septal defect this figure is similar to ours. In the present study chest narrowing with or without a straight spine was associated with the innocent murmurs in 16.7 per cent of the patients with no heart disease. This suggests that chest narrowing is an important cause of innocent murmurs, but because of the preselection of our cases we are unable to determine the incidence of narrow chests without murmurs. Chest narrowing associated with pectus excavatum is also a cause of systolic murmur

It is apparent that the hemodynamic changes with congenital or rheumatic heart disease produce clinical findings which are not altered by the configuration of the spine, the degree of anteroposterior chest narrowing or the attendant distortion of cardiac anatomy (Figs. 4*A* and 4*B*) Many of the patients with congenital lesions had systolic ejection murmurs as a feature of their stenotic lesions or representing flow murmurs across either semilunar valve. Only in one of these (Patient 22 a small ventricular septal defect) did the murmur diminish with deep inspiration The intensity of the pansystolic murmurs of the ventricular septal defect was not influenced by respiration Even with a very narrow chest and a straight spine the diagnostic features of each lesion are apparent and the skeletal change may be considered an unimportant associated finding

The "straight back syndrome" is not commonly seen in children. We have found only two (Patient 22 of the congenital group and Patient 1 of the innocent murmur group) both aged 11 years. De Leon and co-workers[1] reported two patients aged 12 years and two aged 14 years. Serrato and Kezdi[2] reported one aged 14 years. Apparently the murmur of this syndrome is not impressive until growth and development have lengthened and narrowed the chest configuration. This variety of innocent murmur should therefore be sought particularly in patients in the teenage and young adult age groups. In the presence of unexplained systolic murmurs, careful inspection of the back and chest x rays seems indicated. The decrease in intensity of the murmur with inspiration is not specific for chest defor



Fig. 4A. Patient 7 of the CHD group, ventricular septal defect with straight spine and narrow chest. Lateral view of the back showing the straight thoracic spine.



Fig. 4B. Patient 7. The right ventricle and its outflow tract are large and vertically oriented and the distal pulmonary artery is sharply angulated posteriorly.

mities and may be found with any variety of innocent murmur[11]

Summary

In the course of cardiac evaluation of 504 patients known to have heart murmurs particular attention was directed to the configuration of the thoracic spine and chest dimensions An attempt was made to determine the influence of straight spines (absence of the normal thoracic kyphosis) on the cardiac diagnosis of each patient A total of 250 patients had congenital heart disease (CHD) and 200 had rheumatic heart disease (RHD) 54 had innocent murmurs

Of those with CHD 9 2 per cent were found to have straight thoracic spines, an incidence believed due to the tendency of coexistence of several anomalies. The diagnostic features of each heart lesion were not altered by the straight spine and so it may be considered an incidental and unimportant anomaly in these patients There is no apparent association with height weight patterns.

In the patients with RHD straight thoracic spines were encountered less frequently (2 per cent) The physical signs were unaltered in 3 patients with hemodynamically significant valvular problems, and one patient with mild mitral stenosis exhibited the murmur of straight back syndrome

Of 54 patients with innocent murmurs, 9 had anteroposterior chest narrowing and in 4 of these the thoracic spines were straight. The murmur was heard best in the pulmonary area and diminished with inspiration

Although chest narrowing with or without a straight thoracic spine is an important cause of innocent murmurs, organic heart lesions maintain their characteristic diagnostic features regardless of spine configuration

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Coronary artery resection for giant aneurysmal enlargement and arteriovenous fistula

A five-year follow-up

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A broad spectrum of opinion is expressed about the management of coronary arteriovenous fistulas. Almost 70 years have now elapsed since the first surgical correction of a coronary arteriovenous fistula, yet within the last decade one author wrote, "It would be difficult to make a confident diagnosis of coronary arteriovenous fistula during life without resort to an exploratory thoracotomy." Unfortunately, such diagnostic perfections would bring no therapeutic reward, for ligation of the abnormal vessel would carry a grave risk of death from myocardial infarction.

Coronary arteriovenous fistulas continue to be discovered at autopsy or during surgery when an alternative diagnosis had been favored. Nevertheless, as diagnostic measures have now evolved, adequate means are available to establish a diagnosis of this abnormality. Although Björck and Björck[4] state that only 14 such cases have been diagnosed by angiocardiography, selective retrograde arteriography and right-sided cardiac catheterization studies provide quite reliable tools for diagnosis. At the June, 1966, meeting of the Society for Vascular Surgery, Effler and co-workers presented a series of 14 patients with coronary arteriovenous fistulas, all of whom were studied by cinecoronary arteriography. These 14 cases were culled from more than 6,000 selective coronary arteriography studies performed at the Cleveland Clinic. A fifteenth patient described by Effler was found to have a coronary arteriovenous fistula while undergoing surgery for suspected patent ductus arteriosus.

In spite of the infrequency and sometimes complicated nature of coronary arteriovenous fistulas, few major cardiac abnormalities have been so effectively treated by surgery. Of approximately 85 patients operated upon, we know of only 6 operative fatalities.[8]

This report concerns a preoperatively diagnosed coronary arteriovenous fistula

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complicated by a huge right coronary artery aneurysm

Case report

A 46-year-old Caucasian housewif was admitted to the U iversity of Missouri Medical Center in September 1961 with the complaint of "heart trouble Dyspnea on exertion had been present for pproximately 6 months. More recently dyspnea was evident t rest The patient adm tted t a "roaring sound in her chest Paroxysmal nocturnal dyspnea and orthopnea were noted The patient could walk less tha three blocks t time. Twenty five years earlier the patient had been told that she had heart murm r

Physical examination revealed a thin pale dyspneic and pprehe ive woman The blood pressure was 130/80 mm Hg in both arm the pulse was 150 and irregular the respirations were 40 per minute A sy tol he w dible over the entire nterior thorax. A systolic thrill was bilaterally present over the carotid arteries. The neck veins were grossly distended and pulsat le Cardiac d llness extended from the left mid illary line t the right midcla icular line A sy tolic thrill and a loud (Grade IV) almost continuous murmu was present t the pper right sternal margin in the second and third intercostal spaces. There was a Grade II systolic m rmur t the pex. The li er was pulsatile and enlarged 2 cm. below *the right costal margi* in the n idclavicular line.

Pertinent normal laboratory determinations in cluded complete blood count urinalysis, fasting blood sugar blood u ea itrogen and serum elec trolytes.

The admission ECG revealed a mea QRS axis of +120° *marked clockwise rotation i the precordial* leads, atrial fibrillation with a rapid entricular response nd nonspecific ST and T wave hanges. A roentgenogram of the chest showed massi e generalized enlargement of ardiac ilhouett pulmo



Fig. 1A Posterior anterior roentgenogram revealing massively enlarged cardiac silhouette.

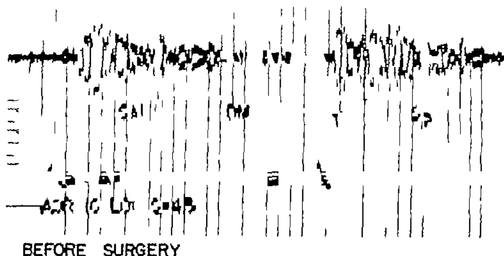
nary congestion, and bilateral pleural effusion (Figs. 1A and 1B). The phonocardiogram demonstrated a continuous murmur t the second right intercostal space (Fig 2).

Right heart catheterization (Table 1) revealed large left-to-right sh t at the trial level Large CV wa es in the right atrial pressure curve indicated tricuspid insufficiency and suggested that the p-parent shunt t the tral level terminated instead in the right entricle, resulting in the entrance of arterialized blood int the right atrium Pericardial effusion as not suspected because the tip of the catheter could be manipulated t within several millimeters of the free all of the right trium.

Retrograde aortography (Figs. 3 4 and 5) demonstrated the passage of contrast material from the ascending aorta into an enormously dilated right coronary artery which occupied the medial portion of the right hemithorax. This essel extended to the diaphragm before ndergoing transition into smaller tortuous vessel which extended into the left hemithorax. A lateral projection of the anomalou coronary artery filled from the orta and extended along the anterior surface of the heart The tortuous



Fig 1B Left lateral roentgenogram revealing massively enlarged cardiac silhouett



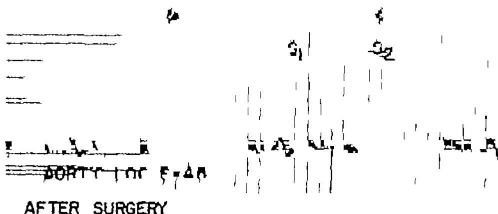


Fig. 2 Preoperative and postoperative phonocardiograms recorded at the aortic area. Note the continuous murmur recorded before surgery (*S1* first sound, *S2* second sound, *SM* systolic murmur, *DM* diastolic murmur.)

Table I Data obtained during cardiac catheterization

Location	*Preoperative*		*Postoperative*	
	O_2 content (vol. per cent)	*Pressure (mm. Hg)*	*O_2 content (vol. per cent)*	*Pressure (mm. Hg)*
Superior vena cava	10.39		13.1	
Right atrium, high	11.34		12.69	
Right atrium, mid	13.27	17/6	12.83	4/(−2)
Right atrium, low	14.69		12.98	
Right ventricle, low	15.55		13.17	
Right ventricle, mid	15.58	64/1 12	13.39	27/(−2)
Pulmonary artery	16.55	48/18	13.76	30/5
Systemic artery	18.13	164/58	18.04	137/72
Cardiac output (c.c./min.)	2196		4720	
Pulmonary artery flow (c.c./min.)	5167		4243	
Per cent left to right shunt	61% of pulmonary blood flow			
Arterial oxygen saturation (per cent)	94.9		95.4	

*Values obtained at separate catheterization.



Fig. 3. Retrograde aortogram using 30 of 50 per cent Hypaque, anteroposterior view. *A*, Orifice of congenital arterial fistula. *B*, Left coronary artery.

segment extended posteriorly and finally entered the heart in the region of the right ventricle.

On admission the patient was given digitalis. The heart rate diminished from 150 per minute to 80 per minute. Surgery was performed on February 9, 1962. The cardiopulmonary bypass unit was in the operating room on a standby basis. Through a sternal splitting incision the pericardial sac was exposed and opened. Approximately 1,000 of yellowish pericardial fluid was removed. The huge coronary artery originated from the aorta superior to the usual point of origin. As it progressed distally in the atrioventricular groove, aneurysmal dilatation (8 to 10 cm. in diameter and 22 cm. in length) extended to the inferior border of the heart. At that point it coiled to the left and posteriorly, continued as a vessel 2 to 3 cm. in diameter and terminated by communication with the right ventricle on the posterior surface of the heart (Fig. 6).

The enormous aneurysmal dilatation of the right coronary artery obscured any demonstrable branches of that vessel. The artery was clamped near its aortic origin and was observed to fill from below. With clamps on the proximal and distal ends of the main portion of the aneurysm it was readily emptied by inserting a large-bore needle. No collateral filling was observed.

With the right coronary artery clamped either near its origin, or at the lower margin of the heart, or at both sites simultaneously, T-wave inversion in the ECG was observed (Fig. 7). Marked slowing of the heart likewise occurred. Following the removal of the clamp these changes promptly reversed. Numerous ventricular extrasystoles also appeared but decreased with each repeat episode of clamping. Finally, after six or seven attempts, the ECG changes appeared considerably less pronounced. From its bed within the groove between the right atrium and the right ventricle, the aneurysm was dissected and resected. A row of continuous sutures was used to close the artery at the points of transection.

Examination of the resected arterial segment revealed rather extensive areas of calcification in the aneurysm wall. The total weight was 26 Gm.

The right atrium diminished markedly in size



Fig 4A Retrograde aortogram using 40 c.c. of Hypaque, anteroposterior view Arrows indicat the course of the large congenital coronary arterial fist la.

upon transection of the aneurysm and the heart rate slowed precipitously

The patient postoperative course was generally uneventful. Daily electrocardiograms, however revealed a persistent current of injury in diaphragmatic leads. The patient was, therefore managed as one with acute myocardial infarction however anticoagulants were not administered. On the fifteenth postoperative day large Q waves evolved in ECG leads 3 and AVF diagnostic of infarction (Fig 2). The cardiac silhouette, although still enlarged was markedly reduced two months postoperatively (Fig 8) nd four years later it was normal. A repeat cardiac catheterization (Table 1) six months post operatively was within normal limits. When last seen, over four years after the operation the patient continued to ppear markedly improved over her preoperative status and she was able to participat in almost all activities about the home

Discussion

Because of considerable variation in the types of fistulas, it would appear ill advised to categorize the coronary artery fistula as a lesion with standard clinical manifestations requiring any entirely uniform method of therapy Conclusions based on a limited perspective may not be warranted for the group as a whole. Coronary artery fistula variations include the following Either the right or left coronary artery may empty into any cardiac chamber pulmonary artery bronchial artery coronary vein or coronary sinus. Consequently the volume of blood shunted is variable Dilatation of the anomalous coronary artery varies significantly The extent of myocardial blood supply from the anomaly varies. Approximately 20 to 30 per cent of the cases are associated with other significant cardiac abnormalities Ten patients had pulmonary valvular atresia.[11] In addition to high out



Fig. 4B. Later sequence showing tortuous course of large coronary aneurysm.

put failures and cardiac enlargements, bacterial endocarditis, endarteritis, anemia and glomerulonephritis have been reported.[14,21,23 25,27,28] Cyanosis may be present.

The findings of a loud to-and-fro murmur and a precordial thrill on palpation should alert one to the possibility of coronary arteriovenous fistula. Retrograde arteriographic studies or direct cinearteriography are invaluable. Cardiac catheterization studies will yield further helpful hemodynamic data.

Cardiac enlargement prompts one to consider the possibility of a patent ductus arteriosus,[19-23] aortic regurgitation associated with a ventricular septal defect, an aorticopulmonary window, a pulmonary arteriovenous fistula, or a ruptured sinus of Valsalva. A subclavian or internal mammary arteriovenous communication may simulate this picture, particularly in the female patient. On the other hand, aneurysms of the coronary arteries without fistula formation are more common in men. Simple aneurysms are three times as common in the left coronary artery as on the right.[34]

The surgical management of the patient with a coronary arteriovenous fistula includes a variety of techniques. In the first reported case, that of Björck and Crafoord, simple ligation of the fistulous tract was accomplished. Most communications have been obliterated by double ligation of the vessel.[3, 8] Some have divided the vessel. Others have performed an arteriotomy and sutured the fistulous stoma. Open-heart surgery with the cardiopulmonary bypass machine has been used with suture

Fig. 5 Retrograde aortogram left lateral view

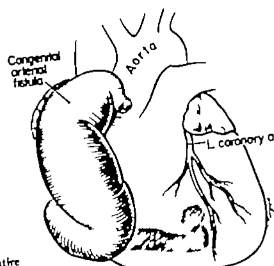


Fig. 6 Sketch of the heart demonstrating the entire course of the congenital arterial fistula as shown by retrograde aortography

Before Surgery | During Surgery | Immediately After Surgery | 15 Days After Surgery | 27 Days After Surgery

I

II

III

AVR

AVL

AVF

V1

V2

V3

V4

V5

V6

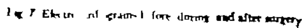

1 ig 7 Electr   ol grams b fore during and after surgery



Fig. 8 Posteroanterior chest film 2 months after surgery

of the fistula from inside the ventricle.[26] Hypothermia combined with cardiopulmonary bypass has been used.[27]

At least four operative cases have been complicated by myocardial infarction either at surgery or within six months postoperatively. Transient electrocardiographic ST and T wave changes indicating possible myocardial ischemia have been reported.

Hallman, Cooley, and Singer[1] have preserved continuity of the dilated vessel by passing multiple mattress sutures tangentially to the posterior surface of the artery and the anterior surface of the ventricle. With lateral arteriorrhaphy, flow through the fistula is halted but blood continues to flow through the artery.

Resection seemed the procedure of choice in our case because of the huge size of the vessel, absence of collateral flow into the vessel during proximal and distal clamping, ability of the myocardium to tolerate clamping, and left coronary collateral flow of sufficient magnitude to maintain viability of the myocardium. The desirability seemed apparent in removing this huge mass with its resultant pressure on the right atrium and ventricle.

Conclusion

Surprisingly enough, coronary arteriovenous fistula appears to be the most com

monly encountered type of coronary artery developmental abnormality In cases exhibiting cardiac failure, myocardial ischemia, bacterial endarteritis, pulmonary hypertension or considerable left to-right shunting the desirability of surgical correction is apparent. In patients with small shunts, minimal cardiac enlargement, and few clinical symptoms, the need for surgical management is less obvious. Some of these patients may live to an advanced age.

The resection of a large right coronary artery aneurysm complicating a coronary arteriovenous fistula to the right ventricle is reported Over 5½ years later the patient is doing well and is asymptomatic. The entire myocardium is apparently being supplied by the left coronary artery

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Renal vascular hypertension, further experiences

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The medical literature contains numerous reports on the selection and successful surgical treatment of hypertensive patients with stenotic lesions of the renal arteries. Nevertheless, it is apparent that not all patients with renal hypertension require or are benefited by operation.[1-4]

At the University of California Medical Center in San Francisco renal arteriograms have been performed in increasing numbers since 1952 in both hypertensive and normotensive patients. Many patients with stenotic renal arterial lesions of different types have undergone corrective operations, and the patients have been followed postoperatively for 2 to 14 years. This report presents a long range evaluation of our arteriographic findings and operative results during the 14 year period since 1952.

Materials and methods

Clinical material All patients with hypertension in whom adequate radiologic visualization of the renal arteries was obtained at the University of California Medical Center between November 1952 and December 1964 were included in this study. Patients were considered hypertensive if their average blood pressure before and during hospitalization exceeded 150/90 mm Hg. On the basis of a complete history, physical examination and routine laboratory studies, each patient was classified according to severity of hypertension (class I through IV) as defined previously.[5] The specific indications for arteriography were variable and reflected the changing ideas over the years. Most of the hypertensive patients had features (clinical and urologic) considered atypical of benign essential hypertension,[1] and the renal arteries were visualized in an attempt to find curable lesions responsible for the hypertension.

The study also includes a number of normotensive patients (blood pressures consistently below 150/90 mm Hg) who were examined by arteriography for evalu

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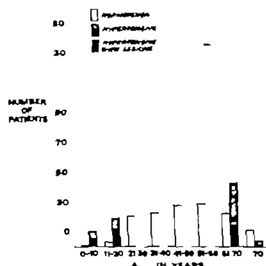


Fig. 1. Age distribution of hypertensive and normotensive patients at the time of renal arteriography.

ation of urologic problems or obscure abdominal pain, for screening as potential kidney donors, in search of primary neoplasms in cases of metastatic or hematologic disease, and for visualization of the aorta in cases of peripheral vascular insufficiency.

A total of 659 subjects were studied: 525 hypertensive patients (235 men and 290 women) and 134 normotensive patients (69 men and 65 women). The distribution of patients according to age is shown in Fig. 1.

Radiologic and urologic technique. Arteriograms were performed by the translumbar or retrograde transfemoral route of Seldinger[11] and in a few cases by the transaxillary route, with either 76 per cent Renografin (diatrizoate methylglucamine) or 50 per cent Hypaque (sodium diatrizoate) as contrast medium. Special attention was given to the performance and interpretation of the intravenous pyelogram. Divided renal function studies were performed with various modifications.[12] They were usually done to determine the significance of lesions found in the arteriogram, although on occasion they were used as a screening procedure before arteriography. Renograms with I-labeled Hippuran (sodium ortho-iodohippurate) were also done in selected cases. The interpretation of this study and the techniques have been summarized by others.[13,14]

Operative management. The indications for surgical management were modified with increasing clinical experience. In the early years of the study, arterial reconstruction was attempted on almost all patients with significant renal arterial lesions (50 per cent occlusive or more). Because of the high mortality rate (both operative and late postoperative), older arteriosclerotic patients were subsequently excluded, with the exception of patients with azotemia caused by operable bilateral renal artery obstruction. The decision to operate on patients with hypertension due to fibromuscular hyperplasia depended primarily on the location and extent of the constricting lesions and whether reconstructive procedures were surgically feasible.

Revascularization procedures were carried out in preference to nephrectomy, except when reconstruction of a unilateral lesion was technically not feasible or the involved kidney was atrophic or hypoplastic. In a few elderly poor risk patients with a unilateral lesion nephrectomy was performed because of the lesser surgical risk involved.

Postoperative observations. All patients were examined at 1 to 2 month intervals until their blood pressure was stable and subsequently at intervals of 6 months to 1 year. Of all patients who were alive 1 month after operation, 69 per cent were observed personally by us; the remaining 31 per cent were examined regularly by their referring physicians, who reported their findings to us.

Patients were classified as improved or unchanged by operation tentatively after 1 week and definitively after 1 year. In all but 3 patients, follow-up examinations have been carried out and are being continued for the detection of late recurrence or complications. Patients were classified as normal if their postoperative blood pressures were consistently below 150/90 mm. Hg on all determinations. They were classified as improved if (1) the mean diastolic blood pressure was consistently lower than the preoperative level by at least 20 mm. Hg, (2) the pressures were

almost always below 150/90 mm Hg with only occasional abnormal readings, (3) only the systolic pressure remained in the hypertensive range or (4) the blood pressure was easily controlled with mild hypotensive therapy where potent drugs had been required or ineffective preoperatively

Results

Arteriographic findings The number of hypertensive patients studied by arteriography at the San Francisco Medical Center has increased progressively with the growing awareness of the frequency of renal vascular hypertension Before 1958 fewer than 10 arteriograms were performed yearly From 1958 to 1960 the yearly number increased from 12 to about 70 and since 1961 more than 100 arteriograms have been done each year From 1952 to 1964 730 renal arteriograms were performed on the 659 patients.

MODIFICATIONS OF ARTERIOGRAPHIC PROCEDURES The majority of arteriograms were performed by the percutaneous retrograde femoral technique. In a very few patients, adequate visualization of the arterial tree was obtained with the initial 5 ml. test dose of contrast medium. In a larger group a single injection of 15 or 30 ml was adequate for diagnosis. In almost half of the patients, however a second or third injection was required to confirm the presence or extent of a suspected arterial lesion In the latter group the patient was often placed in a more oblique position since experience has shown that such positioning permits better visualization of the origin of some renal arteries from the aorta and their separation from superimposed radiopaque structures. In patients with fibromuscular hyperplasia respiratory maneuvers and alterations in posture permitted uncoiling and "stretching of the involved vessels thus defining the extent and degree of stenosis produced by a lesion or associated aneurysm [7]

COMPLICATIONS The major complications from arteriography by each of the three techniques are listed in Table I A total of 46 complications occurred but no patient died or was permanently disabled Retroperitoneal bleeding from translumbar aortography was judged present in 10 cases on the basis of a fall of 10 per cent or more in hematocrit or obscurity or displacement of the psoas shadow or kidney in later roentgenograms, or by direct observation at the time of subsequent operation. In no case was surgical intervention necessary although three patients required transfusions. The single instance of cardiac arrest occurred during general anesthesia but was not fatal Subsequent studies, however were performed under local anesthesia whenever possible.

Two patients had massive and extremely painful spasm of the back and leg muscles immediately after transfemoral injection

Table I Major complications from arteriography in 730 studies on 525 hypertensive patients and 134 normotensive patients

Technique	Complication
Translumbar 155 studies	
Presumed significant retroperitoneal bleeding	10
Transient fall in phenolsulfonphthalein (PSP) excretion	5
Transient hypotension requiring pressor therapy	2
Unexplained prolonged abdominal pain	2
Transient cardiac arrhythmia	1
Transient leg paresthesias	1
Cardiac arrest	1
Total	22
Retrograde transfemoral. 563 studies	
Transient hypotension requiring pressor therapy	6
Allergic reaction	5
Transient arterial spasm	2
Massive spasm and pain in back and leg muscles	2
Transient fall in PSP excretion	2
Prolonged unexplained abdominal pain	2
Preretinal hemorrhage	1
Popliteal artery embolus	1
Subintimal passage of catheter	1
Total	22
Transaxillary 12 studies	
Transient left hemianopsia	1
Paresthesias and pain in ulnar nerve distribution	1
Total	2

of 5 ml and 30 ml of 76 per cent Renografin respectively, transient cord ischemia was thought to be a possible mechanism. In the one patient who had a popliteal embolus after arteriography, the intraluminal passage of the catheter had been smooth and uncomplicated. This patient, a 40-year-old normotensive potential kidney donor, had shown no previous evidence of atherosclerosis. All patients were pretested for sensitivity to the contrast media, but minor allergic reactions did occur in 5 patients.

Minor complications, such as local inguinal hematomas (transfemoral technique), nausea, and extravascular extravasation of contrast media (transfemoral or translumbar technique), were observed relatively often, depending on how carefully they were sought. In no case did these have sequelae or cause prolonged disability. Among the 26 patients with impaired renal function (see below) arteriography did not result in further deterioration of function.

CLASSIFICATION OF ARTERIOGRAPHIC FINDINGS. Patients were considered to have major lesions if the arterial lumen appeared to be approximately 50 to 75 per cent occluded and minor lesions if the narrowing was 50 per cent or less. The lesions were classified as atherosclerotic (AS), fibromuscular hyperplastic (FMH), or miscellaneous. The radiologic characteristics of AS and FMH lesions have been described previously. In the latter group we include the whole range of fibrous and muscular dysplasias of the medial layer of the arterial wall. Whenever both types were present in the same patient (8 cases), classification was based on the dominant lesion. The term miscellaneous was used to designate renal arterial lesions demonstrated by the radiologist but not radiologically characteristic of either AS or FMH. The classification in these cases was based on the operative and microscopic findings.

Hypertensive patients. The results of renal arteriography in the hypertensive patients are listed in Table II. The high incidence (15 per cent) of renal parenchymal disease in the 278 patients with normal renal arteries is consistent with the findings of other investigators. The relationship of the parenchymal lesions to the hypertension in these patients was investigated further only when nephrectomy or other corrective procedures appeared possible.

Of the 525 hypertensive patients, 195 (37 per cent) had major renal arterial abnormalities radiologically. In 95 patients the lesions were classified as atherosclerotic, in 70 as fibromuscular hyperplastic, and in 30 as miscellaneous. The clinical and radiologic features of the patients with

Table II. Renal arteriographic findings in 525 hypertensive patients

Arteriographic findings		No. of patients
Normal renal arteries: 278 patients		
Entirely normal study		
Total		236
Renal parenchymal lesions		
Atrophy		20
Cyst		8
Small vessel disease		5
Solitary kidney		4
Tumor		3
Medullary sponge kidney		1
Hydronephrosis		1
Total		42
Renal arterial abnormalities: 247 patients		
Major lesions		
Atherosclerosis		95
Fibromuscular hyperplasia		70
Miscellaneous		
Unilateral uniformly narrow artery	13	
Renal artery thrombosis (main artery 3, branch artery 1)	4	
Renal artery aneurysm (extrarenal, 2 calcified, 1 noncalcified; intrarenal, 1 noncalcified)	4	
Arteriovenous malformation	3	30
Undiagnosed focal stenosis (main artery 1, branch artery 1)	2	
Idiopathic fibrosis	1	
Intimal fibrosis	1	
Intimal hyperplasia	1	
Dissecting aneurysm of aorta involving renal artery	1	
Total		195
Minor lesions		
Atherosclerosis		34
Fibromuscular hyperplasia		14
Miscellaneous		4
Total		52

Table III. Comparison of clinical and radiologic characteristics of patients with renal arterial stenosis due to atherosclerosis or fibromuscular hyperplasia

Clinical data	*Atherosclerosis*	*Fibromuscular hyperplasia*
Total number	95	70
Male/female	56/39	8/62
Bilateral/unilateral stenosis	47/48	36/34
Unilateral stenosis right/left	30/18	21/13
Severity of hypertension		
Class I	10	26
Class II	40	30
Class III	30	14
Class IV	15	0
Age at time of study (years)		
0-10	0	3
11-20	0	2
21-30	0	14
31-40	6	17
41-50	33	21
51-60	38	10
61-70	16	3
Over 70	2	0
Ocular fundi		
Grade KW IV	12	0
Grade KW III	13	3
Renal function impaired	16	0
Extrarenal vascular disease	53	8

major AS and FMH lesions are compared in Table III. In both groups 50 per cent of the lesions were bilateral though not always equally severe. Extrarenal fibromuscular hyperplasia involving the internal carotid, external iliac, and mesenteric vessels was demonstrated radiologically or at operation in 11 per cent of the 70 patients with renal arterial fibromuscular hyperplasia.[29] Nine patients with fibromuscular hyperplasia had prominent collateral circulation around the stenotic lesion. Among the patients with atherosclerotic renal artery stenosis collateral circulation was rarely observed unless aortic occlusion was present. Although several of the patients with AS lesions were Negro, we have not yet seen a Negro patient with FMH lesions. Patients with AS renal arterial lesions tended to be older men with moderate to severe hypertension; some had renal functional impairment and many had associated occlusive peripheral vascular disease. Patients with FMH lesions tended to be young, otherwise healthy women with mild hypertension and normal renal function.

Thirty patients had miscellaneous renal arterial lesions such as thrombosis, intimal fibrosis, and intimal hyperplasia (Table II). In the 13 patients with a unilateral uniformly small renal artery without focal or segmental narrowing, various types of renal parenchymal abnormalities were suspected. In six of the 13 the suspected lesion was confirmed as congenital hypoplasia, atrophic pyelonephritis, polycystic kidney, or hydronephrosis. Whether the renal artery was small secondary to renal parenchymal atrophy or congenitally small, supplying a hypoplastic kidney, was not clear by arteriography. This difficulty has also been encountered by other investigators.[31]

Normotensive patients. The arteriographic findings in the 134 normotensive patients are listed in Table IV. Renal parenchymal lesions were demonstrated in 39 cases, reflecting the urologic and other indications for arteriography in these patients. Among the normotensive patients both AS and FMH lesions were encountered. A total of 22 patients had major or minor renal arterial lesions resembling those found in the hypertensive patients. It is of interest to note that 7 per cent of the normotensive patients had major stenotic lesions, compared with 37 per cent of the hypertensive patients.

Surgical management consisting of a renal artery reconstruction together with an extensive aortoiliac revascularization was undertaken in only one of the normotensive patients with a major lesion; the normal blood pressure remained normal postoperatively. Pathologic confirmation of the lesions or physiologic studies such as divided renal function studies were not undertaken in the remaining patients.

Multiple renal arteries. Multiple renal arteries supplying one or both kidneys were present in 21 per cent of the hypertensive patients with major arterial lesions, 15 per cent of the hypertensive patients with normal renal arteries, and 27 per cent

Table IV. Renal arteriographic findings in 134 normotensive patients

Arteriographic findings	*Patients*
No abnormalities	73
Renal parenchymal lesions	
Cyst or tumor	32
Atrophy	6
Ureteral obstruction	1
Total	39
Renal arterial stenosis	
Major	
Atherosclerosis	6
Fibromuscular hyperplasia	2
Other	2
Minor	12
Total	22

of the normotensive patients. The importance of accessory renal arteries was emphasized especially when it became apparent that in some cases unrecognized small arteries had been accidentally ligated during an earlier operation on patients who subsequently remained hypertensive. Often these vessels, particularly if very small were not recognized at the time of the initial arteriogram and were noted only after careful review and comparison of the preoperative and postoperative x ray films.

CONFIRMATION OF RELIABILITY OF RADIOLOGIC FINDINGS Of the 278 hypertensive patients with normal renal arteries, 22 were operated on subsequently for renal parenchymal or abdominal lesions 5 were examined at autopsy Although the retroperitoneal operative approach used in most of these cases did not permit palpation of the entire length of the renal artery an attempt was made to feel for "missed" arterial lesions. Only one patient whose arteriogram was interpreted as normal was found to have a palpable renal arterial plaque but without thrill or measurable gradient Removal of this plaque, which even in retrospect could not be recognized on the arteriogram did not result in a fall in blood pressure.

Of the 195 patients with major renal arterial lesions, 12 were subsequently examined at operation and 9 at autopsy and the presence and pathologic nature of the lesion was confirmed in all but one patient. In a few patients classified as having fibromuscular hyperplasia radiologically the lesion appeared more fibrous than muscular on microscopic examination and would have been classified as idiopathic fibrous rather than fibromuscular hyperplasia by some investigators.[22]

Of the 52 patients with minor lesions, 6 were operated on for various reasons. In two patients, a renal arterial plaque was removed by endarterectomy although no gradient or thrill was observed neither had a fall in blood pressure postoperatively In two others, the incidental presence of a small irregularity or plaque in the renal artery was confirmed but since no gradient was detected no further procedure was carried out. In the remaining two patients, palpation did not reveal an abnormality and arteriotomy was not performed In 18 patients with minor unilateral lesions, divided renal function studies were performed and all were negative. Repeat arteriographic studies in a few patients with minor lesions have not shown progressive involvement.

INDICATIONS FOR ARTERIOGRAPHY To assist in the selection of future patients for arteriography we reviewed the clinical and urologic features used for recommending or justifying the procedure in the present series of 525 hypertensive patients. No one feature was pathognomonic of the presence of a major renal arterial lesion When any three of the classic indications were present, such as recent, abrupt onset or acceleration of hypertension epigastric bruit, grade IV Keith Wagener fundi aortoiliac occlusive disease, or positive divided renal function study the likelihood of finding a significant lesion was almost 75 per cent. Even in the absence of all indications except for hypertension however a major arterial lesion was found in four of 27 patients.

Clinical indications Recent onset of hypertension recent increase in severity and negative family history of hypertension all unreliable unless carefully documented were found more often in patients without major arterial lesions than in those with lesions (Fig 2) Onset of hyper

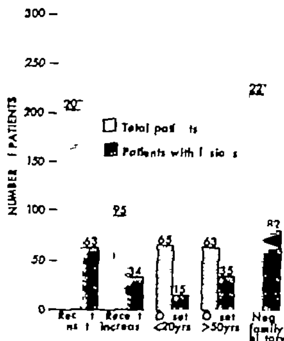


Fig 2 Frequency of atypical historical features of hypertension among patients with major renal artery lesion compared with total group of hypertensive patients.

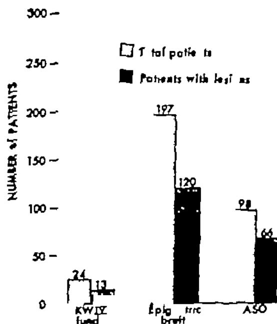


Fig 3 Frequency of certain clinical findings among hypertensive patients with major renal artery lesions compared with total group of hypertensive patients (ASO arteriosclerosis obliterans)

tension before the age of 20 years was likewise *not helpful, but onset of hypertension* after the age of 50 was associated with a major arterial lesion in 55 per cent of patients. Over 60 per cent of all patients with an epigastric bruit or occlusive aorto-iliac disease had major renal arterial stenosis (Fig 3) The epigastric bruit was often localized and its detection required careful listening in a quiet room The high pitched bruit of renal arterial obstruction could usually be distinguished from a transmitted mitral murmur or from the rough short bruit of atherosclerotic aorto-iliac disease which was usually heard widely over the abdomen and femoral arteries. A bruit was detected in 73 per cent of all patients with FMH lesions and in 59 per cent of those with AS lesions, but in less than 22 per cent of patients with *an entirely normal arteriogram The incidence* of arterial lesions was increased with increasing severity of hypertension 47 per cent of patients with class III and IV severity had lesions compared with 33 per cent of those with class I and II severity (Fig 4) Most of the patients with severe hypertension had AS lesions, whereas FMH was encountered in patients with *mild hypertension*

Urologic indications Patients with disparity in the function and size of the two kidneys as shown by intravenous urography were more likely to have a major arterial lesion than patients with disparity only in kidney length (Fig 5) A difference in the length of the kidneys of 1 cm or more or a reversal in the usual left/right size ratio (L > R) was considered significant 43 per cent of patients with these findings had a major renal arterial lesion The disparity in renal size among the patients with normal renal arteries ranged from 0 to 2 9 cm but 72 per cent of these patients had a difference in size of 0 9 cm, or less. Delayed appearance of the contrast medium and poor opacification of one kidney in early films, smaller collecting structures, or delayed excretion associated with late hyperconcentration were seen more frequently (> 50 per cent) in patients with vascular lesions than in those without A normal pyelogram however did not exclude the presence of an arterial lesion In 2 patients with bilateral and in 23 with unilateral lesions no abnormalities

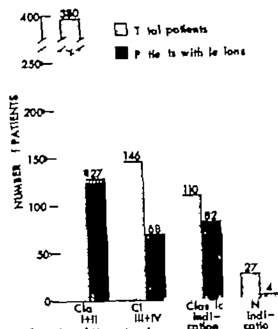


Fig. 4 Severity of hypertension and frequency of classic or no indications for arteriography among patients with major renal artery lesions compared with total group of hypertensive patients.

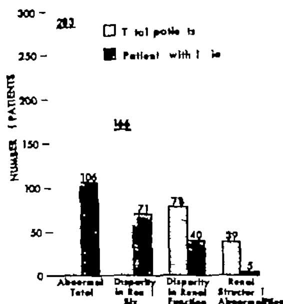


Fig. 5 Frequency of various pyelographic abnormalities among patients with major renal artery lesions compared with total group of hypertensive patients.

were recognized on the intravenous pyelogram. Also in 39 patients in whom intravenous pyelograms indicated a unilateral lesion arteriography revealed a bilateral lesion.

Divided renal function studies were positive in 48 and negative in 99 of the 147 hypertensive patients so studied. Table V shows the correlation between the positive and negative divided function studies and arteriographic findings. When studies were unequivocally positive, the patients had either a vascular lesion or unilateral atrophic pyelonephritis. Negative results, however, were obtained in 22 of 55 patients with significant unilateral arterial stenosis. Most of the falsely negative results were obtained in patients studied before 1961, and it is possible that the use of newer modifications and improved techniques (Stamey) would have provided more accurate results.

The studies were associated with a moderate number of minor but distressing complications: ureteral colic, bladder spasm, hematuria, pyuria, and fever were observed relatively often. Two patients died after the procedure, one within 3 hours, apparently from a ventricular arrhythmia, and the other 3 days after the study, possibly from cerebral edema following urea infusion.

Renograms with [131]I labeled Hippuran were obtained in 65 cases. The reliability of this procedure as compared with the arteriogram, intravenous urogram, and divided renal function study is shown in Table VI. The results were considered equivocal if the only abnormality was an isolated delay in the excretory (free water clearance) or third part of the curve. Both falsely positive and falsely negative results were obtained as judged by the arteriographic findings. With further experience and standardization of the technique and patient preparation (hydration) we may obtain more consistently reliable results.

Surgical techniques and results

OPERATIVE TECHNIQUES. Endarterectomy was the preferred procedure in patients with atherosclerotic stenosis. Since these

Table V. Correlation of results of divided renal function studies with arteriographic findings in 147 hypertensive patients

Divided renal function studies	Arteriographic findings	No. of patients
Positive	Unilateral arterial stenosis	33
	Bilateral arterial stenosis	13
	Unilateral atrophic pyelonephritis	2
	Total	48
Negative	Unilateral arterial stenosis	22
	Bilateral arterial stenosis	18
	Minor arterial irregularities	18
	No abnormalities	41
	Total	99

Table VI. Comparison of results of renography (¹³¹I labeled Hippuran) with other diagnostic studies in hypertensive patients

Comparative study	Renographic findings		
	Positive 31 studies	Equivocal 18 studies	Negative 16 studies
Isotope renogram			
Positive	22	6	4
Equivocal	2	3	3
Negative	7	9	9
Intravenous pyelogram			
Positive	19	12	6
Negative	10	5	10
Not done	2	1	0
Divided renal function			
Positive	10	4	2
Negative	7	7	4
Not done	14	7	10

lesions usually involved only the proximal third of the renal artery they were readily accessible through the open aorta. If the process was unilateral a disk of intima around the orifice of the involved artery was dissected free and removed as a single specimen together with the obstructing intima from the renal artery. If bilateral a cylinder of aortic intima including the orifices of both renal arteries was removed.

Renal shunting procedures (splenorenal anastomosis or aortorenal bypass) for atherosclerotic lesions were employed only when technical difficulties made it hazardous to mobilize the aorta at the level of the renal arteries.

For patients with FMH lesions segmental arterial resection with end-to-end reanastomosis was formerly the preferred procedure. The operation resulted in suture line stenosis in two patients (of 31 so managed) and thrombosis in a third probably due to abnormal tension at the suture line. For this reason segmental resection has been used subsequently only in patients with limited localized lesions. Renal artery replacement or bypass by an arterial autograft has become the preferred technique. The hypogastric artery was found to be an ideal donor vessel for this purpose.[20] In cases in which the constriction of FMH extended into one of the primary branches of the renal artery venous or arterial patch angioplasty was frequently employed. In general however reconstruction was limited to patients with involvement of the main renal artery or the proximal first centimeter of the primary branches. More extensive lesions were considered inoperable unless they appeared to be entirely unilateral and nephrectomy was considered justified.

In general an operation was undertaken if the arterial lesion appeared to be the cause of the hypertension. A lesion more than 50 per cent occlusive (radiologically) especially if associated with evidence of decreased renal function by pyelography or divided renal function study was presumed to be a hypertension producing lesion.

OPERATIVE RESULTS. The results of surgical management were evaluated on the basis of blood pressure measurements 1 year after the operation. Patients who died at operation or while hospitalized postoperatively were classified as operative deaths. Of the 195 hypertensive patients with major renal arterial lesions, 122 were operated on and of these 79 (65 per cent) sustained a significant fall in blood pressure—37 per cent to normal levels (Table VII).

Table VII. Evaluation of operative results based on blood pressure levels 1 year after renal arterial reconstruction or nephrectomy in 122 hypertensive patients

	Atherosclerosis	*Fibromuscular hyperplasia*	*Miscellaneous*	*Total*
Total operated patients	66	42	14	122
Postoperative blood pressure				
Normal	15	24	6 }	79
Improved	22	8	4 }	
Not improved	18	9	2	29
Deaths	11 (7)	1 (1)	2 (2)	14 (10)

Numbers in parentheses are operative deaths

Atherosclerotic lesions. Of the 95 patients with atherosclerotic lesions 66 patients underwent a total of 70 vascular operative procedures. The unilateral procedures included unilateral thromboendarterectomy (25 cases—in 2 of these a subsequent nephrectomy was performed because of restenosis), spleno–left renal arterial anastomosis (2 cases), and nephrectomy (9 cases). Bilateral procedures included bilateral thromboendarterectomy (25 cases) and one case each of spleno–left renal arterial anastomosis with subsequent second stage right nephrectomy, spleno–left renal anastomosis with right renal artery thromboendarterectomy, unilateral thromboendarterectomy and contralateral nephrectomy, and bilateral thromboendarterectomy with segmental nephrectomy. One patient had a thromboendarterectomy followed by a left nephrectomy 7 years later because of restenosis, followed by a right autogenous bypass graft 6 years later and this was subsequently replaced by a Dacron bypass graft. Additional aortoiliac surgery, including thromboendarterectomy or replacement grafts, and bilateral lumbar sympathectomy were performed in 25 of these patients. Three additional patients were found to have inoperable lesions at laparotomy. Among the 27 patients with unilateral revascularization procedures, 48 per cent had a fall in blood pressure with an operative mortality rate of 15 per cent. By contrast among the nine patients who underwent simple nephrectomy 89 per cent had a fall in blood pressure with no operative deaths.

Of the 66 operated patients with atherosclerotic lesions 15 (23 per cent) had a sustained postoperative blood pressure fall to normal and 22 (33 per cent) were improved over their preoperative level (Table VII). In 18 patients the blood pressure was classified as unchanged at the end of the first year after operation. Possible causes of the sustained hypertension (singly or in combination) were extensive generalized atherosclerosis (6 cases), underlying renal parenchymal disease by history or biopsy (7 cases), residual inoperable arterial lesion (3 cases), postoperative evidence by arteriography of occluded accessory or branch renal artery (2 cases), restenosis of main artery due to thrombosis or progressive disease (2 cases), and systolic gradient across stenotic segment at the time of operation of less than 25 mm. Hg (2 cases). Five of seven patients with unilateral lesions and negative preoperative divided renal function tests had no fall in pressure postoperatively. In 4 patients no reasonable explanation for the failure was found either by postoperative arteriography or careful review of all available data. In these cases it may be assumed that the atherosclerotic plaque was either incidental to or not the only cause of the hypertension since the presence of unrecognized peripheral arterial lesions cannot be excluded.

Table XIII. Reliability of blood pressure levels 1 week and 1 year postoperatively in evaluating the results of surgical treatment in patients with renal arterial lesions

	1 week after operation		1 year after operation			
			Blood pressure			Dead
	Blood pressure	No. of patients	Normal	Improved	Not improved	
Atherosclerosis 59 patients (surviving)	Normal	19	8	8	2	1
	Improved	14	5	8	1	0
	Not improved	26	2	6	15	3
Fibromuscular hyperplasia 42 patients	Normal	18	13	4	1	0
	Improved	13	7	3	3	0
	Not improved	10	4	1	5	1
Miscellaneous 14 patients (12 surviving)	Normal	7	4	2	1	0
	Improved	3	2	1	0	0
	Not improved	2	0	1	1	0

Seven operative deaths occurred. In 3 cases, the cause was renal failure associated with hemorrhage, shock, and anuria; in one case each, the cause was cardiac arrest during the operation, uremia secondary to thrombosis of the reconstructed artery, perforated peptic ulcer, and cerebrovascular accident and acute coronary occlusion. Four additional patients, only one of whom had had a postoperative fall in blood pressure, died before the end of the first postoperative year: one of cerebrovascular accident, two of myocardial infarction, and one of congestive heart failure.

The rate at which the blood pressure fell postoperatively was variable. In 29 of the 37 patients who were classified as normal or improved at the end of one year (Table XIII), the fall in blood pressure occurred during the first week after operation. In the remaining 8 patients there was a delayed fall in blood pressure up to 6 months after operation. Eight patients had a complicated and difficult postoperative course including a period of oliguria and impaired renal function followed by massive diuresis and electrolyte depletion. These patients eventually recovered.

Of the 55 patients who survived the first year after operation, all but 3 have been followed until the present time. Of the 15 patients classified as normal, one died of a myocardial infarction 5 years after operation and one developed restenosis of both the operated and the contralateral renal arteries 7 and 13 years later, responding to reoperation in both instances, but dying finally of progressive renal failure. Of the 22 patients classified as improved, two died of myocardial infarctions 4 and 7 years later, respectively. Of the 18 patients not benefited by operation, 4 have died between 2 and 4 years after operation, one of a brain tumor and the other 3 of progressive cardiovascular renal decompensation.

Lesions due to FMH. Of the 70 patients with major lesions due to FMH, 42 underwent 44 operative procedures—23 unilateral segmental resections (one patient subsequently underwent nephrectomy for restenosis at the anastomosis site), four patients had bilateral segmental resections and one of these underwent subsequent nephrectomy for thrombosis at one suture line, five bypass grafts, two vein patch grafts, one patient had a bypass graft on one side and segmental resection on the other in two stages. Eight patients underwent nephrectomy for technically inoperable unilateral arterial disease.

Nephrectomy was avoided in patients with possible bilateral lesions and employed only in cases of inoperable unilateral main or branch artery lesions, but the results compared favorably with those obtained with revascularization procedures. Eight of the 10 nephrectomies resulted in postoperative improvement while only 20 of the 29 patients with unilateral revascularizations were improved

The rate of fall of the blood pressure in the patients with FMH was variable but the majority of patients with a normal blood pressure at the end of the first week after operation remained improved (Table VIII)

Of the 42 patients operated 24 (57 per cent) had a fall in blood pressure to normal and 8 (19 per cent) were significantly improved (Table VII) One of these patients had a postoperative cerebrovascular accident, although her blood pressure had fallen to normal levels immediately after operation. She has a residual hemiparesis and aphasia, but remains normotensive. Late recurrence of hypertension has occurred in one "normal" patient precipitated by toxemia of pregnancy two years after operation Four patients with unilateral lesions had secondary hyperaldosteronism corrected in each case by reconstructive vascular surgery All 8 patients who had a significant fall in blood pressure but not to normal levels, had a minimal lesion on the contralateral side which was not operated on. One of these had an acute cerebrovascular accident 5 years after operation she remains mildly hypertensive

In the nine patients (21 per cent) whose pressures did not fall, the presumed causes (singly or in combination) were inoperable major arterial lesion on the contralateral side (four cases) postoperative occlusion of a renal artery branch with segmental infarction (four cases) renal biopsy evidence of arteriolar sclerosis or chronic pyelonephritis in the contralateral kidney (two cases) pressure gradient of 25 mm Hg or less across the stenotic segment (two cases) and residual stenosis at the anastomosis site (one case) In two of four patients with unilateral lesions and negative divided renal function tests preoperatively the blood pressure did not fall. At the present time the hypertension of most of the unimproved patients is moderately well controlled by medical treatment.

One patient died 17 days after an apparently successful operation from rupture of an unsuspected vertebral artery aneurysm

Miscellaneous vascular lesions Only 14 of the 30 patients with miscellaneous abnormalities of the renal arteries were operated on (Table VII) Eleven patients had a nephrectomy one patient had a thromboendarterectomy and subsequent nephrectomy for restenosis a year later one patient had a repair of an arteriovenous fistula and one patient had a thromboendarterectomy on the right and nephrectomy on the left. Of these 14 operated patients 10 (77 per cent) were benefited. One patient with unilateral renal artery intimal hyperplasia had secondary hyperaldosteronism which was corrected after renal artery reconstruction. The two patients who showed no change in blood pressure after nephrectomy had bilateral lesions one died of progressive renal failure 20 months after the operation. Two patients with extensive inoperable lesions, one with multiple arterial emboli and one with congenital intimal hyperplasia of the aorta and its branches, died shortly after operation. One additional patient was examined surgically but no gradient was found a preoperative Howard study had been negative She died 8 months later of a cerebrovascular accident at autopsy the explored kidney showed a large cortical scar

Factors relating to surgical results

Divided renal function studies The correlation between the results of preoperative divided renal function studies and the results of operation is shown in Table IX. Although inconsistencies occurred, probably due to technical difficulties and inadequacies in the earlier studies, a positive study was usually associated with a postoperative fall in blood pressure (94 per cent of the patients surviving one year) whereas a negative study was associated with a postoperative fall in only 39 per cent of patients surviving one year

Preoperative renal function Of the 195 hypertensive patients with major vascular lesions 26 had impaired renal function Of

Table IX. Correlation of results of preoperative divided renal function studies with blood pressure changes 1 year after operation in patients with renal arterial lesions

Divided renal function studies		Type of lesion	Postoperative blood pressure		Dead
			Normal or improved	Not improved	
Positive	39 patients	Unilateral	26	1	1
		Bilateral	8	1	2
Negative	25 patients	Unilateral	6	8	1
		Bilateral	3	6	1

Table X. Postoperative improvement in renal function 1 year after renal arterial reconstruction in patients with impaired renal function

Patient	Preoperative		Postoperative		
	Serum creatinine (mg./100 ml.)	PSP excretion (per cent at 30 min.)	Serum creatinine (mg./100 ml.)	PSP excretion (per cent at 30 min.)	Blood pressure
C. C.	2.6	15	1.4	20	Improved
L. D.		15		40	Normal
M. D.	3.2		2.2		Improved
R. F.	2.1		1.3		Improved
A. H.	1.9	10	1.7	25	Normal
P. J.	2.0		1.8		No change
R. I.	1.9	5	1.6	35	Normal

these 18 had moderately severe impairment of over-all renal function as indicated by a serum creatinine greater than 1.6 mg. per 100 ml., creatinine clearance of less than 50 ml. per minute, PSP excretion of less than 25 per cent in 30 minutes, or blood nonprotein nitrogen (NPN) retention greater than 50 mg. per 100 ml. The remaining 8 patients had milder but definite renal functional impairment.

Of the 26 patients with impaired renal function, 22 had atherosclerotic lesions, one had multiple emboli associated with bacterial endocarditis, and 3 had a unilateral uniformly small renal artery with underlying atrophic pyelonephritis; none had fibromuscular hyperplasia. Eleven of the 26 patients had bilateral and 15 had unilateral renal vascular lesions. All of the latter, however, had evidence of contralateral pyelonephritis, long-standing hypertension, extensive atherosclerosis, or premalignant or malignant hypertension.

Corrective operative procedures were performed in 15 patients. Ten were definitely benefited: in 7, renal function improved (Table X), and in 3 others renal function stabilized and the blood pressure levels fell or were more easily controlled. Six of the 10 patients who were eventually benefited had a complicated postoperative course with transient further deterioration of renal function and oliguria followed by massive diuresis. Five of the 15 operated upon died, 3 from operative complication and 2 from progressive renal failure.

Postoperative improvement in kidney status was observed not only in patients with initially impaired over-all renal function but also in those with normal over-all function. Fifty-one atherosclerotic patients with normal renal function under

went operation, a postoperative increase in the size or function of the kidney on the revascularized side was demonstrated in 8, and in 2 a positive divided renal function study became negative. (Divided renal function studies, however, were not usually repeated postoperatively.)

None of the patients with fibromuscular hyperplasia had impaired renal function. In a few cases the urine contained small amounts of protein and occasional white cells. Of the 42 who underwent operation, 8 had a postoperative increase in the size of the revascularized kidney; in 2 the divided renal function study became negative. In another 5 patients the revascularized kidney decreased in size postoperatively. On the basis of postoperative arteriography the decrease was attributed to segmental infarction resulting from ligation or thrombosis of small branch or accessory renal arteries during operation. Massive diuresis occurred in occasional patients with fibromuscular hyperplasia after revascularization procedures as in the patients with atherosclerosis.

Microscopic evidence of renal disease. In this series of patients, biopsies of both kidneys were not performed routinely at the time of operation. In 31 patients with AS lesions, 13 with FMH and 15 with miscellaneous lesions, however, renal tissue obtained by biopsy, nephrectomy, or autopsy was examined microscopically.

Of the 31 AS patients (average age, 54 years) all but two had microscopic evidence of moderate to advanced arteriolar sclerosis in the kidney distal to the stenotic renal artery, as well as in the contralateral kidney. In six this was associated with chronic pyelonephritis. Twenty patients with evidence of nephrosclerosis survived the operation; of these, 14 had a fall in blood pressure. Tubular degeneration secondary to ischemia was rarely present.

Microscopic examination of renal tissue from the 13 patients with FMH showed no evidence of severe nephrosclerosis. Six of the patients (average age, 39 years) had mild arteriolar sclerosis; the remaining 7 (average age [illegible]3 years) had no arteriolar disease. Associated pyelonephritis was found in two of the former group and one of the latter. All 13 underwent operation and, except for the patient who died, all had a fall in blood pressure postoperatively. Bilateral renal biopsies were available in 8 patients with predominantly unilateral lesions. No characteristic difference could be discerned between the "protected" or "ischemic" and the contralateral kidney, nor was the tubular degeneration characteristic of ischemia recognized.

Miscellaneous factors. The clinical features and results of operation were compared in patients with unilateral and with bilateral lesions (Table XI). Among the patients with bilateral lesions, fewer had operable lesions, the results were poorer, and the mortality rate was higher than in the patients with unilateral lesions. The patients with bilateral FMH lesions were older on the average than those with unilateral lesions. In patients with both AS and FMH lesions those with bilateral lesions had a longer average duration of hypertension than those with unilateral lesions.

The surgical results were related to the average age and duration of hypertension in patients with AS and FMH lesions. Although the mean age was somewhat greater and the duration of hypertension longer in the patients whose blood pressure did not fall, the differences were not significant. It is of note, however, that some patients with up to a 12 year history of hypertension were "cured" by the operation.

Fate of patients not operated upon. A total of 72 patients with major arterial lesions did not undergo revascularization procedures or nephrectomy, 29 with AS, 28 with FMH, and 15 with miscellaneous lesions. The reasons for avoiding operation were: technically inoperable bilateral lesions (apparent on the arteriogram or discovered at laparotomy), extensive atherosclerosis in the cerebral or coronary arteries, associated incurable systemic or renal parenchymal disease, moderately stenotic arterial lesions in patients with mild hypertension amenable to medical control, and a negative divided function test in patients with a unilateral lesion. In two cases, the patients were returned to their referring physician for operation.

Fourteen (19 per cent) of the 72 patients not operated upon have since died. Ten

Table XI. Correlation of clinical features and surgical results 1 year after operation with type of lesion in patients with major renal arterial lesions

	Atherosclerosis		*Fibromuscular hyperplasia*	
	Unilateral	*Bilateral*	*Unilateral*	*Bilateral*
Total patients	48	47	34	36
Average age (years)	53	53	34	41
Renal functional impairment	5	11	0	0
Duration of hypertension in years (average)	5	8	4	6
Total operated upon	33	31	23	19
Blood pressure lowered	22	15	19	13
Blood pressure unchanged	9	9	3	6
Died	4	7	1	0
Total not operated upon	11	18	11	17
Died	4	6	0	2

therosclerotic patients died, 9 within one year of study. The causes of death included miscellaneous noncardiovascular disease (3 cases), progressive renal failure (2 cases), dissecting or ruptured aortic aneurysm (2 cases), cerebrovascular accident (one case), and acute myocardial infarction (one case). Two of the patients with FMH died, one of a coronary thrombosis and one presumably from cerebral edema resulting from urea infusion during a divided renal function test. Two with miscellaneous lesions have died. One was the patient described previously who underwent renal artery exploration but no definitive corrective operation; the other patient died of acute bacterial endocarditis.

Discussion

The high incidence of significant occlusive lesions of the renal arteries in this group of selected hypertensive patients confirms the importance of renal vascular disease as a potentially curable cause of hypertension. Of 525 hypertensive patients studied, 195 had major arterial lesions, 122 were operated on, and of these 76 had a subsequent fall in blood pressure, 45 to normal levels. Thus, almost 9 per cent of the entire group may be said to have had curable renovascular hypertension.

Because of the slight but definite risk involved in renal arteriography, even by the transfemoral route, various methods of screening patients for arteriography have been suggested. We have found none of these completely reliable. Patients with numerous indications for renal arteriography may fail to have an arterial abnormality, whereas others with no indications for study may have correctible lesions. Arteriography is seldom a routine part of the initial evaluation of hypertensive patients. Since renal hypertension does not differ in its initial manifestations from essential hypertension, however, the physician must consider the possibility in every hypertensive patient. Screening tests that compare the two kidneys may be misleading because, if both kidneys are diseased, the test may not indicate any disparity in their size or function. The results of the present evaluation suggest that patients should be studied by arteriography if they have severe hypertension, especially with evidence of recent acceleration, if they have an abdominal bruit, disparity in renal size and/or function, and if they are young and potentially good operative candidates, should a lesion be found. In older arteriosclerotic patients arteriograms should be performed only if the hypertension is severe and if associ-

ated diseases do not preclude operation should a correctible lesion be found If renal function is impaired in patients without known renal parenchymal disease, arteriography should be considered to exclude a correctible vascular lesion The procedure is usually of no value in screening obese, older patients with long-standing mild uncomplicated hypertension because they are rarely candidates for operation. If an intravenous urogram is abnormal and especially if it shows the classic ischemic pattern the patient should be examined by arteriography A normal urogram however may be obtained in patients with bilateral lesions and should not be a deterrent to arteriography unless other contraindications exist. A positive renogram or divided renal function study also indicates the need for further investigation, but negative studies do not rule out a correctible arterial lesion or lesions.

The 7 per cent incidence of major arterial abnormalities in patients without hypertension stresses the need for establishing the physiologic significance of a stenotic lesion in hypertensive patients before corrective surgical procedures are considered In patients with unilateral lesions a "positive divided renal function test or a grossly abnormal [131]I Hippuran renogram is reasonably reliable evidence of an ischemic kidney as the probable cause of the hypertension In cases of bilateral lesions, physiologic function studies are of little value unless the lesion on one side predominates. Other methods have been used to differentiate lesions that produce ischemia from those that do not. The percentage of occlusion can be estimated radiologically but this measurement may be misleading The presence of poststenotic dilatation or collateral circulation has been attributed to an ischemia producing lesion, but neither is always present in proven cases. Only if the blood pressure falls after correction of a demonstrated vascular lesion is it possible to attribute the hypertension to the presence of the lesion. Even the measurement of renin or angiotensin in the peripheral or renal vein blood has been misleading since the circulating levels of these substances are not always increased even in proven cases of renal hypertension.[34-36]

The exact role of renal arteriolar sclerosis or involvement of interlobular arteries in initiating or maintaining hypertension remains unresolved. Although some investigators have suggested that surgical correction of the stenosed main renal artery is of little value in patients with biopsy evidence of arteriolar sclerosis or decreased renal plasma flow in the contralateral kidney [7] we have found exceptions to this generalization. It is probable that the degree of arteriolar sclerosis determines the operability of a lesion. At this time we do not know at what degree of arteriolar sclerosis operation becomes futile Renal vascularization procedures, however are carried out not only to lower the blood pressure but also to improve renal function in patients with bilateral preocclusive lesions and renal functional impairment In these cases the presence of renal parenchymal or arteriolar disease should not preclude revascularization attempts.

The question arises whether all hypertensive patients with arterial stenoses that could reasonably be considered the cause of the hypertension should undergo operation If the lesion is operable the patient relatively young and in good health and the hypertension severe the answer should be yes. Patients with renal impairment resulting from bilateral lesions should be operated on because otherwise the prognosis is extremely poor Older patients with mild hypertension are not good surgical candidates, especially if they are obese or diabetic or have cerebral or coronary atherosclerosis, since the operative risk is high and the need for lowering the pressure frequently is not urgent. In these patients medical therapy is often adequate and therefore preferred. Also the atherosclerotic plaque may be a result of long-standing hypertension rather than the initial cause and unless the abrupt closing of a renal vessel has produced malignant hypertension revascularization may be of no benefit

The exact operative technique used in each case must depend on the discretion and ability of the surgeon and the clinical condition of the patient. Constant reevaluation of techniques is important, as is periodic restudy of operated patient to learn the outcome of anastomotic pro-

Arrhythmias associated with the synchronous pacemaker

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Implantable cardiac pacemakers have become the preferred form of treatment for patients with uncontrollable Stokes-Adams attacks due to third degree A-V block. Recent technologic advances have made available an internal cardiac pacemaker that synchronizes atrioventricular activity.[1-4] In these instruments an additional circuit detects the electrical activity of the atrium and transmits it to an amplifier which triggers the pacemaker. This refinement over the asynchronous pacemaker provides a more physiologic way of overcoming complete heart block. Synchronous pacing restores autonomic control over the ventricular rate and optimum cardiac output by re-establishing the normal temporal relationship between atrial and ventricular contractions. In order to avoid complications arising from atrial arrhythmias or from failure of the synchronizing device several safety features have been incorporated. These include a standby pacer which automatically takes over if an atrial signal is not received within a specific time interval, a delay circuit to simulate normal atrioventricular conduction time, and a blocking mechanism to limit the maximum rate.

In the 9 month period between April 1965 and January 1966, 13 synchronous pacemakers were implanted in patients at the University Hospital in Saskatoon. Eight of these developed some form of arrhythmia in the immediate postoperative period. These disturbances in rhythm produced complicated electrocardiographic changes. It is the purpose of this paper to analyze these arrhythmias and to suggest how the pacemaker may have functioned under these conditions.

Materials and results

The pacemaker used in all of our patients was the Atricor.[4] This pacemaker consists of two assemblies: a pacer which is enclosed in a hermetically sealed plastic casing and the atrial and ventricular lead systems which are enclosed in silicone and rubber (Fig. 1). The atrial electrode which is sutured to the epicardial surface of the left atrium is capable of picking up any P wave potential above 0.9 mv. This impulse is transmitted to the pacer where it is amplified and after a delay of 0.16 second a 2.0 msec, 6.5 volt impulse is delivered down an output wire to initiate ventricular depolarization. The pacer has a refractory period of 0.44 second during

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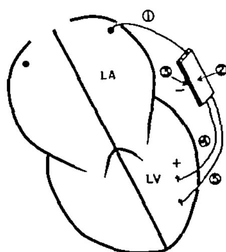


Fig 1 Diagram of an implanted synchronous pacemaker 1 Atrial lead 2 pacemaker box 3 ground plate 4 active ventricular lead 5 spare ventricular lead

which it cannot be triggered In the event of an inadequate atrial signal a sinus rate below 50 or 60 malfunction of the atrial electrode or single battery failure a standby oscillator circuit begins pacing at a fixed rate of 60 per minute. If the rate rises above 103 to 107 a refractory delay will automatically induce a 2 1 or 3 1 block and slow the ventricular rate There is a spare ventricular lead which can be switched on should the active lead fail Thus, this instrument successfully by passes the atrioventricular block by providing an external mechanism to replace the faulty myocardial conduction.

The electrocardiograms of patients with an Atricor pacemaker show a normal relationship between the P wave and the QRS complex. The stimulus artefact produced by the electrical discharge of the pacemaker falls at the beginning of the QRS complex. The time interval between the P wave and the stimulus artefact is called the P-spike interval The contour of the QRS usually has a modified right bundle branch block configuration because depolarization originates in the left ventricle All ECGs taken after a pacemaker was implanted were carefully reviewed for arrhythmias. These may be classified under the following headings pre-excitation of the ventricles by the pacemaker premature beats, atrial flutter and fibrillation atrial pacemaker block and activation of the pacemaker by premature ventricular beats.

Pre-excitation of the ventricles by the pacemaker Following the implantation of a pacemaker conduction through the A V junction may improve or return to normal possibly as a consequence of better coronary perfusion A V conduction is occasionally faster than the conduction through the pacemaker Four of the five cases in which this occurred had presented with intermittent A V dissociation due to block. In most instances the ventricles were completely depolarized by normal impulses and the pacemaker stimulus (falling in the absolute refractory period of the ventricles) was ineffective However one patient showed some evidence of pre excitation of the ventricles by the pacemaker Fig 2 shows a portion of the record taken one day after the pacemaker was implanted. There is marked variation of the atrial rate. The first second tenth and eleventh atrial beats originate in the sinus. The P waves are followed by the stimulus artefact of the pacemaker and the corresponding ventricular depolarization. The third fifth and seventh beats occur early (because they are ectopic atrial beats, or because of sinus arrhythmia or both) These three beats are followed by normally conducted ventricular complexes. The P R interval (0 16 second) is shorter than the P-spike interval (0 20 second) and the stimulus artefact of the pacemaker of these three beats falls after the inscription of the initial or entire part of the ventriculogram These pacemaker impulses do not elicit ventricular depolarization because the ventricles are in the absolute refractory period However the contour of the fourth and sixth ventricular complexes shows characteristics of both the normally conducted beat (third fifth and seventh) and the ones produced by the pacemaker (first second tenth and eleventh) Beats four and six therefore are ventricular fusion beats of the type seen in the ventricular pre-excitation syndrome. After the seventh beat there is a period of slowing of the sinus and the pacemaker does not receive an atrial signal in time to prevent the auxiliary pacer from firing The eighth and ninth

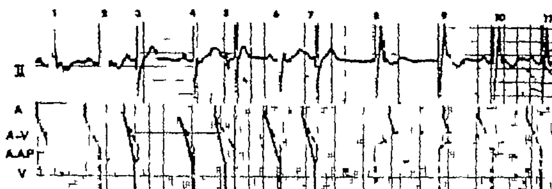


Fig 2 Records of patient w th pre-excitation of the entricles by the artificial pacemaker Beats 1 2 10 and 11 are sus orgin nd conducted through the pacemaker Beats 8 and 9 are pacemaker escapes. Beat 3 5 nd 7 are onducted to the ventricles through the normal A V junction (the pacemaker impulses do not depolarize the ventricles because of ts refractoriness) Beats 4 and 6 are fusion beat The ventricles are depolarized by the mpulse which is conducted simultaneously through both the A V junction and the artificial pacemaker 1 Atrial acti ation A V A V conduction A A P acti ation of the artificial ventricular pacemaker V entricular activation solid line conduction through the normal conducting system broken line conduct on through the artificial pacemaker solid line plu broken line ventricular fusion beats.

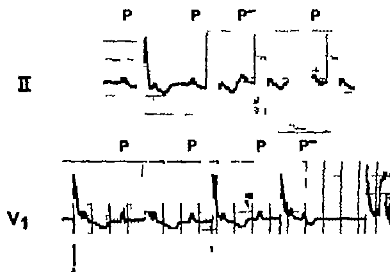


Fig 3 Records of t patient th trial premature be ts (P). For further discussion see text

beats are pacemaker escapes. We can offer no explanation to account for the fact that the escape interval of the eighth beat is shorter than the ninth Similarly we have no explanation for the al normal prolongation of the I spike interval of the fifth beat

Premature beats Premature atrial and ventricular beats were an incidental finding in the record of seven patients. Fig 3 sho vs tracings of two patients who had frequent premature atrial beats. The upper record shows a regular sinus rhythm with all beats conducted through the artificial electrical pacemaker The third I wave which is premature is followed by a stimulus artefact and a ventricular depolariza tion The lower record also shows a regular sinus rhythm except for the fourth I wave which is premature Th is atrial pre

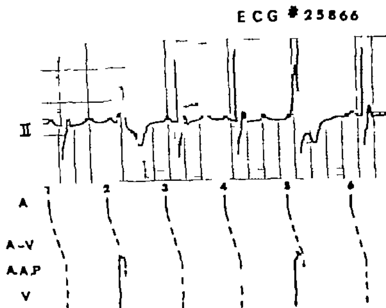


Fig. 4. Synchronous pacing interrupted by ventricular premature beat. For further discussion see text.

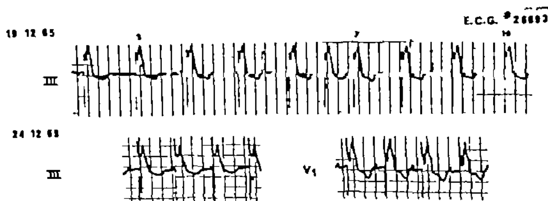


Fig. 5. Upper strip: Atrial fibrillation with asynchronous (beats 1 to 5 and 10) and synchronous (beats 6 to 9) ventricular pacing. Lower strips: Same patient after conversion to sinus rhythm with quinidine. For further discussion see text.

mature beat is not transmitted through the pacemaker because it falls in the refractory period of the delay circuit. It is followed by a pacemaker escape because the next P wave occurs too late to prevent the auxiliary pacer from firing. Two ventricular premature beats are found in Fig. 4. The pacemaker spikes which are triggered by the antecedent P waves, fall within or after the QRS complexes. They have no effect on ventricular depolarization because they arrive during the ventricular refractory period.

Atrial flutter and fibrillation. One patient developed atrial flutter and three others developed atrial fibrillation in the immediate postoperative period. The f waves had sufficient electrical potential to trigger the pacemaker intermittently.[7] The result was a combination of asynchronous and synchronous pacing. The upper strip of Fig. 5 was taken from the ECG of a patient

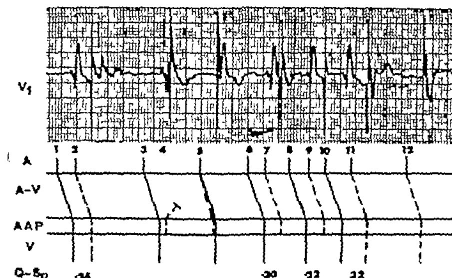


Fig. 6. Atrial fibrillation associated with normal A-V conduction. Beats 1, 3, 5, 8, and 10 are conducted through the normal A-V junction. All pacemaker impulses are triggered by f waves except beat 4, which is a pacemaker escape. Beat 2 shows aberrant ventricular conduction. In the diagram some f waves (1) have been arbitrarily selected to illustrate the origin of an impulse that can conduct either through the normal A-V junction or through the pacemaker. The A-V conduction time (A-V) also has been arbitrarily considered to be approximately the same for every beat. *Q-Sp*, Q-spike interval. Other conventions as in previous figures. For further discussion see text.

who began fibrillating on the second postoperative day. The sixth, seventh, eighth, and ninth beats in this tracing are produced by f waves triggering the pacemaker, while the rest are pacemaker escapes. Atrial fibrillation in another patient also began on the second postoperative day and was associated with some degree of normal A-V conduction. The competition between the artificial and normal conducting system resulted in a bizarre ECG. A combination of normal, pacemaker, and aberrantly conducted pacemaker escape beats is seen in Fig. 6. The first, third, fifth, sixth, eighth, and tenth beats are conducted through the normal A-V junction and result in ventricular complexes with a right bundle branch configuration. Most of the pacemaker impulses are triggered by the fibrillation waves, although there is one escape stimulus artefact (number four). With the exception of the second, eleventh, and twelfth beats, the pacemaker impulses are totally ineffective because they reach the ventricles during their absolute refractory period. The second beat is aberrantly conducted because the stimulus coincides with the the ventricular relative refractory period. The Q-spike intervals of the ineffective pacemaker impulses are all shorter (0.20 and 0.22 second) than the Q-spike interval of the second beat (0.24 second) while in the effective impulse, the Q-spike interval is longer (0.32 second). The fifth beat that begins with a pacemaker spike is conducted through the normal A-V junction. The artificial stimulus did not capture the ventricles, because of its latency.

All the patients with atrial flutter or fibrillation converted to regular sinus rhythm either spontaneously or with the use of digitalis and quinidine.

Atrial pacemaker block. The patients who had no complications, except for the occasional premature beats, had P-spike intervals between 0.16 and 0.18 second.

In four patients the pacemaker conduction time became longer during the follow-up period. These eventually developed complete atrial pacemaker block and asynchronous pacing. The fourth

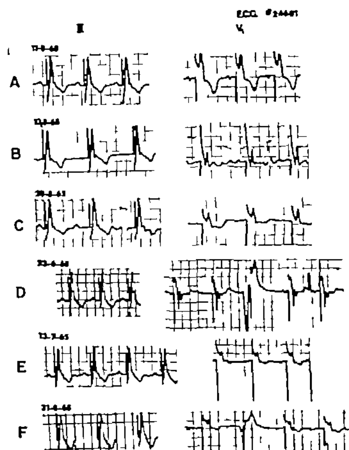


Fig 7 Records of patient who developed permanent atrial-pacemaker block. *A* Immediately after implantation of the synchronous pacemaker. *B* Atrial fibrillation with asynchronous pacing. *C* Sinus rhythm with complete atrial-pacemaker block. *D* Sinus rhythm with intermittent atrial-pacemaker block. *E*, Sinus rhythm with prolonged P-spike interval. *F* complete atrial-pacemaker block. The patient died six months later (see text and Fig. 8)

patient showed a transient episode of atrial-pacemaker block which lasted two months. The records in Fig 7 were taken from a patient who developed atrial fibrillation on the second post-operative day. Strip *A* shows the record immediately after the implantation of the pacemaker. During the period of atrial fibrillation the electrocardiogram showed asynchronous pacing (*B*). When he spontaneously converted to sinus rhythm two weeks later asynchronous pacing continued (*C*). One month later the tracings showed intermittent periods of both synchronous and asynchronous pacing. In Lead II (*D*) the P waves are triggering the pacemaker at an interval of 0 22 second. This is 0 02 second longer than the P-spike interval of the first strip which was taken the day after the pacemaker was implanted. In V_1 (*D*) the pacemaker has reverted to fixed rate pacing. All of the pacemaker impulses are escapes except the fifth which is triggered by the preceding P wave. The third complex is a ventricular premature beat followed by an escape stimulus artefact which does not depolarize the ventricles. In Strip *E* taken three weeks later synchronous pacing is completely restored although the pacemaker conduction time is still prolonged to 0 22 second. Six weeks later the patient reverted back to asynchronous pacing (*F*). Six months after the implantation he noted a slow pulse without any clinical symptoms. He was hospitalized elsewhere and died suddenly the day after admission. The ECG obtained showed a failure of both the atrial

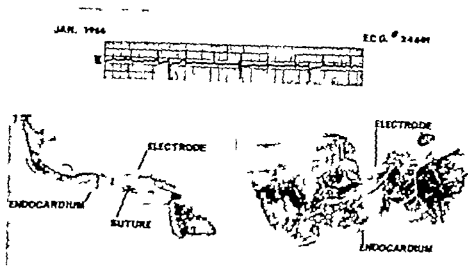


Fig 8 The upper portion of this figure shows the ECG of the patient whose tracing has also been shown in Fig. This tracing was obtained the day before he died. There is complete triloventricular dissociation due ...mplete A V block The electrical artefacts of the artificial pacemaker are seen regularly spaced throughout the record They do not stimulate either the atria or the ventricles. The rate of the artificial pacemaker ... before indicating failure of the power pack The lower portion of the figure shows sections of the left atrium (on the left) and the left ventricle (on the right) Fibrosis is observed around the areas where the electrodes were implanted.

and the ventricular portions of the pacemaker In addition the pacemaker rate was accelerated indicating failure of the power pack. At autopsy sections of the heart showed areas of fibrosis around both the atrial and the ventricular electrodes (Fig 8)

The second patient to develop a complete and permanent atrial-pacemaker block followed a pattern similar to the one described above However approximately five weeks after implantation he died suddenly At autopsy an acute myocardial infarction was found Sections of the left atrial wall showed marked fibrosis and necrotic tissue surrounding the pacemaker implantation site

Fig 9 illustrates a similar series of events in the third patient who developed complete atrial-pacemaker block. Strip A was taken before the pacemaker was implanted. It shows second-degree A V block with 2 1 A V conduction and left bundle branch block. The patient had frequent Stokes-Adams attacks. In Strip B all sinus beats are conducted through the artificial pacemaker with a P-spike interval of 0 16 seconds. In Strip C all beats are normally conducted because conduction through the normal pathway is now faster than through the pacemaker (the P R interval is 0 15 second and the P-spike interval is 0.20 second) Therefore, the pacemaker impulses have no effect on depolarization of the ventricles. Strip D was taken six months later when the patient reverted to asynchronous pacing because of complete atrial-pacemaker block. The patient continued doing well despite this complication but eleven months later developed Stokes-Adams attacks. The ECG showed intermittent failure of the ventricular portion of the pacemaker The power pack was changed and regular synchronous pacing was re-established (E)

Activation of the pacemaker by ectopic ventricular beats The synchronous pacemaker has a spare ventricular lead which is normally inactive In two patients, the electrical potential of ectopic ventricular beats appeared to have triggered the pacemaker by retrograde conduction along this accessory ventricular lead Fig 10 shows three strips from a long record of one patient with this phenomenon This patient had a transvenous pacemaker which was unsatisfactory because the bipolar electrode was not properly positioned Prior to a

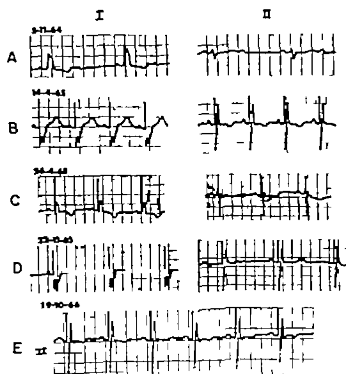


Fig. 9. Progressive prolongation of the pacemaker conduction time with period of normal A-V conduction, ending in permanent asynchronous pacing. *A*, Records obtained before pacemaker implantation. *B*, shortly after implantation (P-spike interval 0.16 second). *C*, conduction through the normal A-V junction (P-spike interval 0.20 second). *D*, complete atrial-pacemaker block. *E*, after implantation of new power pack, synchronous pacing was restored (P-spike interval 0.18 second).



Fig. 10. Three strips of a long record obtained in one of the patients who showed activation of the pacemaker by ventricular ectopic beats. *P*, P waves. ↓, stimulus artefacts of the transvenous pacemaker. 1 and 1, ventricular premature beats from different foci. See text for further discussion.

sertion of an Atricor synchronous pacemaker this bipolar electrode still connected to the power pack was pulled out of the right ventricle into the superior vena cava. It was not removed completely because of the patient's clinical condition. The stimulus artefacts of the transvenous pacemaker (*A*) are independent of the P waves, ventricular complexes and stimulus artefacts of the Atricor pacemaker. There is sinus arrhythmia. The Atricor pacemaker is initiating ventricular depolarization but has reverted to asynchronous fixed rate pacing because of complete atrial pacemaker block. The escape interval is constant at 0.96 second. Frequent ventricular ectopic beats (I–V?) originating from two different foci are also seen. Each of these ventricular ectopic beats is followed by a stimulus artefact of the Atricor pacemaker. The interval between the ventricular ectopic beat and the stimulus artefact is constant (approximately 0.16 second). Furthermore the interval between these stimulus artefacts and the preceding artefacts of the Atricor pacemaker varies and is shorter than the normal pacemaker escape interval (0.76 versus 0.96 second). These three facts have led us to believe that the electrical impulse is conducted up the spare ventricular lead and is triggering the pacemaker. The absence of any relationship between the P waves and the ventricular ectopic beats suggests that retrograde atrial activation with conduction through the atrial lead and subsequent discharge of the pacemaker is not the cause of this phenomenon.

Discussion

The Atricor synchronous pacemaker has proved to be a reliable instrument for the correction of complete or intermittent A-V block with Stokes-Adams attacks in 13 patients. Eight patients developed some form of arrhythmia, usually in the immediate postoperative period. Serious arrhythmias had no permanent consequences with the exception of the three patients in whom the atrial portion of the pacemaker failed.

Premature beats did not interfere with the function of the pacemaker and were entirely benign. Supraventricular premature beats triggered the pacemaker if the impulse reached the pacemaker after its refractory period and were blocked if they arrived during this period (Fig. 3). Ventricular premature beats resulted in the usual aberrant QRS complex, accompanied by the pacemaker spike which was initiated by the sinus impulse.

Flutter and fibrillation waves may have sufficient electrical potential to trigger the pacemaker intermittently. When this potential is inadequate or when the f waves do not reach the atrial pick-up, the pacemaker will revert to fixed rate pacing. The f waves may also be conducted through the A-V junction and compete with the pacemaker for control of the ventricles. If there is no conduction through the A-V junction and if the f waves do not stimulate the atrial lead, the pacemaker will revert to asynchronous pacing (Figs. 5, 6 and 7).

Prolongation of the atrial pacemaker conduction time above 0.20 second could be considered the equivalent of first degree A-V block. Transient episodes of permanent atrial pacemaker block with asynchronous pacing may develop in these patients (Figs. 7, 8 and 9). Failure of synchronization may be due to (1) inadequate or absent atrial signal, (2) interference with transmission of the sinus impulse to the atrial pickup, (3) breakage or damage of the atrial wire, or (4) power pack failure. With the exception of power pack failure, all of these causes should result in asynchronous pacing. The reasons for the failure of synchronization in three patients who developed permanent atrial-pacemaker block seems to be different. In the first it was thought to be due to a combination of battery failure and tissue reaction around the atrial pickup (Fig. 7 and 8). In another patient, who died from a myocardial infarction five weeks after implantation, it was thought to be due to fibrosis around the atrial electrode. In the third patient it was clearly due to failure of the power pack (Fig. 9). Patients with prolongation of the P-spike interval or with complete atrial pacemaker block should be followed closely in order to avert possible fatal Stokes-Adams attacks in the event of battery failure. Transient atrial pacemaker block may occur in the

immediate post-operati e period. This could be due to edema at the implantation site with transmission interference of the P wave to the atrial pickup

Normal A V conduction must be faster than conduction through the pacemaker if it is to capture control of the ventricular rhythm. This is most likely to occur when the atrial pacemaker conduction time is prolonged When normal conduction is restored as in five of our patients, the synchronous pacemaker provides an accessory atrioventricular pathway We anticipated the occurrence of pre-excitation of the ventricles analogous to the Wolfe-Parkinson-Wh te syndrome. This seemed to occur only f the pacemaker stimulus reached the ventricles shortly before the normally conducted impulse. When both stimuli reached the ventricle simultaneously or when the normally conducted impulse initiated ventricular depolarization, the pacemaker stimulus appeared to be ineffective Normal conduction probably supersedes the artificial electrical stimulus because it is transmitted through the Purkinje system while the pacemaker impulse is aberrantly conducted and has a short latent period. Fusion beats, which occur only if both systems contribute to ventricular depolarization, were rare in patients with synchronous pacemakers.

Activation of the pacemaker by premature ventricular beats is a very interesting phenomenon (Fig 10) From a clinical standpoint no serious consequences were found in the two patients in whom this phenomenon was observed. The stimulu artefacts following the premature ventricular beat occur so early that no ventricular depolarization follows. Of interest is the fact that these patients had complete atrial-pacemaker block when this was observed Further studies to clarify the mechanism of this phenomenon are indicated

Summary

The synchronous nternal cardiac pacemaker was designed to offer a more physiologic means of correcting complete A V block. Eight of the 13 patients who had this instrument implanted at the Uni versity Hospital in Saskatoon developed some form of arrhythmia three with atrial fibrillation one with atrial flutter one with transient and three with permanent atrial pacemaker block. In addition five patients had intermittent periods of normal A V conduction and seven had occasional premature beats. In two patients ectopic ventricular beats appeared to have trig gered the pacemaker by retrograde con duction along the accessory ventricular lead. The behavior of the pacemaker the electrocardiographic changes, and the possible causes of these arrhythmias are discussed.

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Experimental and laboratory reports

Qualitative effects of thoracic resistivity variations on the interpretation of electrocardiograms: The "Brody" effect

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That the resistivity of the tissues of the thorax varies and that these variations have an effect on the interpretation of the electrocardiogram has been known ever since the time of Einthoven. Among studies of the resistivity of thoracic tissues are those of Kaufman and Johnston, Burger and van Milaan, Schwan and Kay, and more recently Rush, Abildskov, and McFee. In this last study, attempts were made to reconcile differences in the results of previous investigations. Many studies of the effects of these variations have been made: to cite a few, the phantom constructed by Burger and van Milaan, the fluid mappers of McFee, Stowe and Johnston, the teledeltos paper models of Brody and Romans, the sectional model of Nelson, theoretical models, and the computer models employed recently by Gelernter and Swihart, and others. Notwithstanding the utility of these studies, we do not have at the moment accurate estimates of the lead fields of electrocardiographic leads. Furthermore, the outlook for obtaining an accurate quantitative evaluation of electrocardiographic leads from any of these models is not encouraging.

For example, attempts to improve on the analogue type model of Burger and van Milaan have met difficulties in simulating the muscle anisotropy and the wide span of resistivity, e.g., 160 ohm-cm. for blood and 2000 ohm-cm. for lung. Although significant progress has been made in both the analogue and digital methods, models complex enough to mimic all the resistivity variations realistically will be cumbersome and expensive to change in size and shape. In this connection McFee and Larungao,[11] using a homogeneous rectangular tank, have made an investigation of 21 different body shapes. To do this with a model more closely conforming to the shape of the torso and simulating resistivity variations and anisotropy would, with present techniques, be a more than monumental task. Furthermore, other complicating factors, such as differences in the thickness of surface muscle layers, introduce substantial variabilities in lead sensitivities, etc., that have not as yet been investigated at all.

It is clear that what is needed at this time is insight into the general effects of the variations of tissue resistivity. The writers, in their work on electrocardio-

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graphic leads, have developed over a period of years a number of viewpoints of this sort which are based on analyses of extremely simple models. In these models the effects of a difference in resistivity are considered one at a time rather than all simultaneously. While still approximate this approach can represent a significant improvement over a homogeneous configuration. The purpose of the series of articles of which this is the first is to present these viewpoints and the associated models.

Perhaps the most striking effect of the variations of the resistivity of the chest tissues on the interpretation of electrocardiographic leads is the "Brody" effect. This effect[a] produces an accentuation of electromotive forces (EMFs) oriented radially and an attenuation of the effects of EMFs oriented tangentially. It arises because of the lower resistance of blood relative to that of heart muscle. One aim of this first article is to describe a "thin shell" model of heart muscle. This model is used to explain the Brody effect in a simple way with the use of lead fields, and to show with it that the Brody effect also applies to the septum. With the thin shell model the effect of anisotropy of heart muscle is also considered. It is shown that anisotropy has little influence on the Brody effect for endocardial elements of heart muscle.

Calculations are also made using a thick shell model. In these the average magnitude of the Brody effect is estimated for vectorcardiographic leads; heart muscle is assumed to be isotropic. The anisotropy of muscle is also considered with the use of a thick shell model. It is shown that this anisotropy roughly halves the Brody effect for muscle elements at or near the epicardium.

Thin shell analysis for free wall of heart

We will first use as our mathematical model of the heart a homogeneous sphere (of blood) surrounded by a thin spherical shell (heart muscle) of lower conductivity. We assume that both are immersed in an infinite homogeneous conductor of still lower conductivity (lung) and that we are interested in the voltages produced by

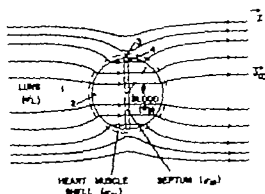


Fig. 1. Thin shell and thin disk model for blood, heart muscle, and lung.

the heart's EMFs in a lead whose two electrodes are located equally remote from the heart on opposite sides of it.

That the heart muscle is not in reality precisely a thin spherical homogeneous isotropic shell in an infinite homogeneous conductor goes without saying. Nevertheless, we feel that this model is sufficiently realistic to give one a qualitative insight into the effect of the changes in resistivity, even though it is only a rough approximation of reality.

As is well known, a lead having two remote electrodes will produce in the general vicinity of the heart a uniform lead field. However, in the immediate vicinity of our low resistance sphere of blood, the lines of current flow of the lead field will be drawn into it, as is indicated in Fig. 1. This concentration of the field lines will strengthen the field in front and in back of the sphere, while at the same time it weakens it at the sides. To estimate the maximum and minimum field strength we therefore determine the field at the points *1* and *3* indicated in Fig. 1.

We have assumed that the spherical shell of muscle is very thin. If this is so, the potential drops produced in it by the current field will be negligibly different from those which would exist were it to have the same resistivity as lung. This means that the flow of current through the shell and the potential gradient along it will not be disturbed by the presence of the shell. In particular, the component of current directed perpendicular to the shell surface will be the same in the

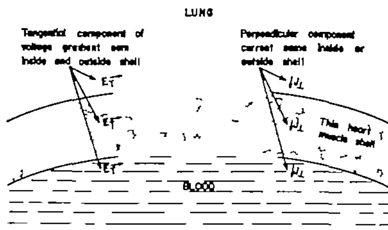


Fig. 2. Equality of tangential potential gradient and perpendicular component of lead field current for thin shell of heart muscle.

outside (Fig. 2). Also the component of potential gradient within the shell directed tangentially to the shell surface is the same in the shell as in lung or blood. But this last implies, since $\vec{J} = \sigma\vec{E}$ for isotropic linear conductors, that if the tangential component of the current field in the blood is J_{Tb} then the tangential component J_{Tm} of the field in the muscle shell will be $(\sigma_m/\sigma_b)J_{Tb}$ where σ_m and σ_b are the conductivities of muscle and blood respectively. The conclusions of this paragraph can be rigorously derived from the equations of the Appendix.

The field which exists in the homogeneous sphere of blood under these circumstances is a uniform field. This well known fact is proved in the Appendix. We will designate its magnitude as J_b. The strength of J_b is greater than the strength of the uniform field in the lung at great distances from the sphere of blood.

Thus, referring to Fig. 1 the field at point 3 is (σ_m/σ_b) times the field J_b at point 4. Thus the ratio of the two is σ_m/σ_b. If we take for $\sigma_m = (1/\sigma_m)$ to be the mean of the high and low resistivities of anisotropic heart muscle (250 ohm-cm.) and (550 ohm-cm.) which is 400 ohm-cm.) and take the resistivity of blood to be 160 ohm-cm., we see that the ratio of maximum to minimum field is 2.5 to 1. As the maximum field occurs where it is oriented radially with respect to the surface of the sphere of blood and the minimum where it is tangentially oriented we have thus derived the Brody effect.

Thin shell analysis for the septum

In a similar manner the septum lead field can be approximated by assuming the septum to be a thin disk immersed in blood throughout which a uniform lead field J_b exists at points outside the disk. Once again it is implied that the disk is so thin that it does not disturb the field outside of it. In this case there are two extreme values for the lead field in the septum. If the field in the blood is oriented perpendicular to the septum (Fig. 3A) the current density in the septum will be the same as that in the blood. On the contrary if the applied blood field is parallel to the septum (Fig. 3B) the field in the septum is reduced by the muscle-blood conductivity ratio of 2.5 to 1. If the applied field meets the septum at some other angle it can be resolved into the two components considered above. The field components in the septum can then be found in terms of these applied field components and the resultant septum lead field obtained by vector addition. It thus appears that the range of lead field strength of 2.5 to 1 in the heart free walls is duplicated in the septum. This, in turn, implies a septal Brody effect causing the reduction of the effects of EMFs tangential to the blood and augmenting the effects of perpendicular EMFs.

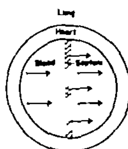


Fig 3A Brody effect for the septum lead field perpendicular to septum. Uniform in blood and septum, equal in strength.

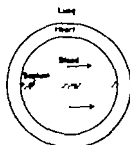


Fig 3B Brody effect for the septum lead field parallel to septum. Uniform in blood and septum strength in septum (160/350) times that in blood.

Thin shell analysis of the effect of anisotropy

Measurements[4] have indicated that the resistivity of heart muscle along the muscle bands which wrap around the heart is lower than across the direction of these bands. Because of the intricate structure of the wrapping an exact analysis is all but impossible. The situation is sufficiently complicated that gross simplifying assumptions are required to make any computation possible. As the heart muscle bands run by and large tangential to the surface of the free walls of the heart and the septum overlapping and crossing each other in various directions, we will assume that in over all effect resistivity is low tangentially and high radially. Thus the anisotropy acts much like that which would be produced by a great number of very thin concentric spherical shells of alternately low and high resistivity. The tangential conductivity of heart muscle we will take to be the mean of the measured low and high conductivities (350 ohm cm).[4] The radial resistivity we will take to be the higher resistivity 550 ohm-cm. Using these assumptions, we ask then what effect such anisotropy would have on our thin shell (free wall) and thin disk (septum) model.

As before, the normal component of the field does not depend on resistivity and will be unaffected by the increased radial resistance. Furthermore the tangential component will be unchanged since the tangential resistivity is unchanged. Thus the amount of the Brody effect is not altered by the increased radial resistivity in the anisotropic thin shelled model.

Thick shell analysis to determine an average value of the Brody effect (without anisotropy)

The heart-blood mass is now to be treated using a model based on two concentric spheres in an infinite homogeneous conductor.

The lead field current once again tends to converge towards the low resistivity heart blood mass from the high resistivity lung. A precise expression for the magnitude of current density $\vec{J}_m$ in the muscle region of our model of the heart is found in the appendix to be given by

$$(\vec{J}_m/J_b) = \left(\frac{\sigma + 2\sigma_m}{3\sigma}\right)\vec{u} + \left(\frac{\sigma - \sigma_m}{3\sigma_b}\right)\left(\frac{a}{r}\right)(2u\cos\theta + \vec{u}_\theta\sin\theta) \quad (1)$$

Here J_b is the strength of the uniform current fields ($J_b\,\vec{u}$) that exists in the blood sphere. σ_b, σ_m, σ_L are the conductivities of blood heart muscle, and lung respectively. The radius of the blood sphere is a and of the outer spherical surface of heart muscle b. The variables, r, θ and z are indicated in Fig 1 and have associated unit vectors u_r, $\vec{u}_\theta$, and $\vec{u}$ pointed in the direction in which these variables increase.

In the above equation the first term on the right hand side represents a uniform field the second a dipole field. Note that the latter is zero if the conductivity of blood and muscle are the same. Note also that this equation is the same as it would be were heart muscle and lung to have the same conductivity. The only effect of a difference between σ_m and σ_L is on the ratio

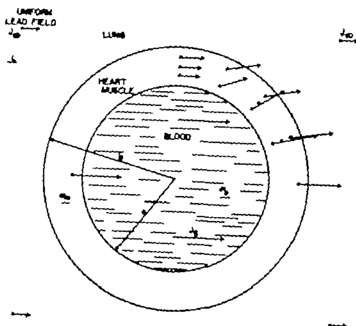


Fig. 4. Thick shell model of heart muscle showing points at which lead field was evaluated and values of fields found there.

of J to J where J_∞ is the field at great distances from blood and muscle. In the Appendix it is shown that this ratio is given by

$$J \quad J = \left(\frac{1}{3} + \frac{2}{3}\frac{\sigma_L}{\sigma_b}\right) + \frac{2}{9\sigma_b\sigma_m}$$
$$\left(\frac{}{b} - 1\right)(\sigma_m - \sigma_L)(\sigma - \sigma_m) \qquad (2)$$

Note that the presence of the muscle shell makes itself felt only if (a l) is different from 1 that is, if the shell is not thin. If the shell is very thin a ≅ 1 this equation shows that the field J is not influenced by σ_m that is by the muscle shell confirming the use of this assumption in the thin shell analysis given previously.

Taking σ to be [160 ohm-cm] σ_L to be [2 000 ohm-cm] and σ_m to be [400 ohm-cm] and evaluating the field J_m at the points shown in Fig. 4 we find the following. First the largest field $J_m = J_b$ occurs at $\theta = 0°$ and 180° and $r = a$ that is at the inner surface of the muscle shell. The smallest field $J_m = \frac{2}{5} J_b$ occurs at $r = a$ and $\theta = 90°$. The largest directional error 26 occurs at the blood muscle boundary at $\theta = 56$. The RMS error in magnitude was determined by evaluating $(|\vec{J}| - \vec{J_m})$ where $\vec{J_m}$ is the weighted average of the magnitude $|\vec{J}|$. The weighting accounts for the increased volume of tissue as r and θ goes from 0 to 90°. The points at which $\vec{J_m}$ was evaluated are shown in Fig. 4. The RMS error in magnitude was found to be 26 per cent and the RMS error in angle 11.

Thick shell analysis with anisotropy

The preceding thin shell analysis of anisotropy of heart muscle may be extended to thick shells using the principle derived in the Appendix. This principle states that the field in the blood sphere will be uniform regardless of anisotropy. As a consequence if the requirement that the normal current density of the lead field and its tangential potential gradient be continuous across the boundary is applied to the inner surface of the thick shell the results obtained with the thin shell are again found. Thus, in the thick shell model we conclude that the higher radial resistivity does not alter the degree of the Brody effect so far as endocardial muscle elements are concerned.

However this conclusion is not true for epicardial muscle elements. Suppose there were a very high radial resistivity. This would make the heart tend to behave like an insulator. In this case lead field current rather than being sucked into the heart would have to make a detour around it. The tangentially oriented current density in the lungs at the sides of the heart would then be higher than the radially oriented current at the front and back. Furthermore, the tangential current density in the lungs at the sides will be magnified in the heart by the ratio of the tangential heart muscle conductivity to the conductivity of lung. Thus the maximum tangential lead field in the epicardial elements could be very much greater than the maximum radial current density. In essence anisotropy can produce a reverse Brody effect insofar as epicardial muscle elements are concerned.

We can analyze this by considering the heart to be made up of a great number of concentric shells of alternately high and low conductivity (Fig. 5, *a*). We will assume that the high-conductivity shells have the same conductivity as blood and the low a conductivity of (720 ohm-cm)$^{-1}$. If we let the high conductivity shell have a thickness of 30 per cent of the combined thickness d of one low σ shell and one high σ shell (thus the low σ shell has a thickness of 0.7d), then we compute an average radial resistivity for two such shells.

$$\rho_r = 0.3\ (160) + 0.7\ (720) = 552 \simeq 550 \text{ ohm cm}$$

and their average tangential conductivity

$$\sigma = 0.3\left(\frac{1}{160}\right) + 0.7\left(\frac{1}{720}\right) = [352]^{-1} \simeq [350 \text{ ohm-cm}]^{-1}$$

These figures correspond fairly closely to the assumptions made previously.

With these figures we are in a position to use Eq. (5) of the appendix to compute successively the fields in shells of increasing radius arriving eventually at the lung. We can then find the field in heart muscle using the familiar boundary conditions, and the known lung and tangential heart muscle conductivities. Of course more work is needed to make the calculations if there are more shells. We therefore will use as few as possible. Fig. 5, *b* shows how the calculation may be made with one low-conductivity shell and Fig. 5, *c* how it may be done with two such shells. We have carried out the calculations in both cases and obtain the same result within 1 per cent, which shows that one shell is adequate. We find that if the field inside in the blood sphere is taken as one, the field in the lung at the heart surface has a maximum radial value of 0.82 and a maximum tangential value of 0.12. To find the field inside heart muscle, the latter should be multiplied by the conductivity ratio (2000/350), yielding 0.69, which is about 15 per cent less than 0.82.

If the heart were isotropic with resistivity of 400 ohm-cm, these values would be 0.76 and 0.51, respectively, the latter being about 30 per cent less than the former. Thus, for epicardial muscle elements the reverse Brody effect has reduced the Brody effect to approximately half its isotropic value.

External fields of closed double layers

Because of the Brody effect radially oriented EMFs within heart muscle can produce external fields several times larger than tangentially oriented EMFs. We may ask: Does this mean that the external fields generated by closed electromotive surfaces of uniform potential difference will no longer exactly cancel one another so that closed EMF electromotive surfaces will have external fields?

The answer is, no. That closed electromotive surfaces produce zero external fields does not depend upon the fact that the conductor in which they are immersed is infinite, homogeneous, or isotropic. All that is required is that there exist one solution to the field for one configuration of sources of it, that is, that the solution be unique. When there exists a closed electromotive surface of uniform potential difference, one possible solution which always applies is that the current inside is zero and the potential there is therefore uniform, that the current outside is zero and the potential there is un... and that the difference in ... en inside and outside is equal ... ial

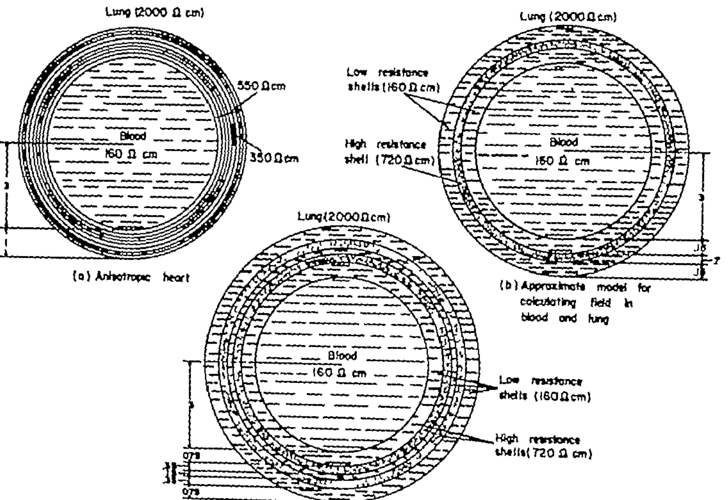


Fig. 5. Approximate models for computing the field *outside* an anisotropic heart. The anisotropy is represented by layers of alternately high and low conductivity. The low and high-conductivity layers are then separated and lumped together. Results computed with the more finely grained model (c) are almost identical to those obtained with (b) indicating that (b) is adequate.

difference of the double layer Since, when a solution is unique, any solution must be *the* solution, a closed electromotive surface will therefore produce no current flow outside of it.

That the solution for the field will be unique in isotropic conductors is well known. Its uniqueness in anisotropic conductors is intuitively evident and may be justified mathematically.[11] What is not clear at the moment is that the potential difference across the electromotive surface is the same regardless of the direction of propagation relative to the axis of the heart muscle fibers. It seems likely that there will exist some variations in the strength of this potential difference although they may be small enough to be neglected. Although measurements of the voltage of the electromotive surface have been made recently additional measurements are needed to clarify this point.

Conclusions

We wish to emphasize again that the models used here are elementary and the results obtained with them are intended only to indicate the order of magnitude of the effects.

Using an isotropic thick shell model for heart muscle we find that the Brody effect produces on the average an RMS change of 11 in the apparent direction of an EMF and 25 per cent in its apparent magnitude. With our thin shell model we find that the Brody effect also applies to the septum We find that anisotropy of heart muscle does not alter the Brody effect insofar as endocardial elements of heart muscle are concerned but it does roughly halve it in the epicardial region.

Appendix

The lead fields in concentric spheres of different conductivity when the remote field is uniform

A sphere of blood (outer radius a σ = [160 ohm-cm.]$^{-1}$) is surrounded by a spherical shell of muscle (outer radius b σ_m = [400 ohm-cm.]$^{-1}$) which is in turn immersed in an infinite homogeneous lung σ_L = [2000 ohm-cm.]$^{-1}$ The lead field at infinity is assumed to be uniform in direction $\vec{u}$

We wish to determine the field in the muscle. We will do this by assuming that the field within the blood sphere *is* uniform. Using the boundary conditions at the spherical interfaces between media of different conductivity we will compute the field further and further out eventually arriving at infinity where we will show that it is uniform thus justifying our assumption

Our analysis[7] will be speeded if we first note the equation for the current density 5-J and the potential V associated with a uniform current field of strength *A* amperes per square meter It is

$$\vec{J} = A\vec{u} \quad V = (AZ/\sigma) = -(A/\sigma)\, r \cos\theta \quad (3)$$

We also note the equations of the field and potential of a current dipole having a maximum strength of unity at a distance R

$$\vec{J} = \left(\frac{R}{r}\right) (\vec{u} \cos\theta + \frac{1}{2}\vec{u} \sin\theta) \qquad (4)$$

$$V = (1/2\sigma)\,(R^3/r^2)\cos\theta$$

The potential in both cases is measured with respect to the $\theta = \frac{\pi}{2}$ plane.

Next we consider the case where the sphere containing either the uniform or dipole field is immersed in another media of different conductivity σ The boundary condition that the normal component of current and the potential be the same at adjacent points on either side of the boundary can be satisfied if we assume that the field in the outer medium is a combination of a uniform field and a dipole field of proper magnitudes. For example if we are given in the inner sphere a uniform field of unit strength A = 1 then one can quickly derive from the boundary conditions just stated and the equations for the uniform and dipole fields that the uniform component of the field in the outer region will be $(\sigma + 2\sigma)/3\sigma$ and the maximum radial strength of the dipole component, at the surface, will be $(2 - 2\sigma)/3\sigma$

In a similar way on can consider the case where the inner sphere has within it the dipole field given by Eq (4) Matching boundary conditions here require that the uniform component of the current field

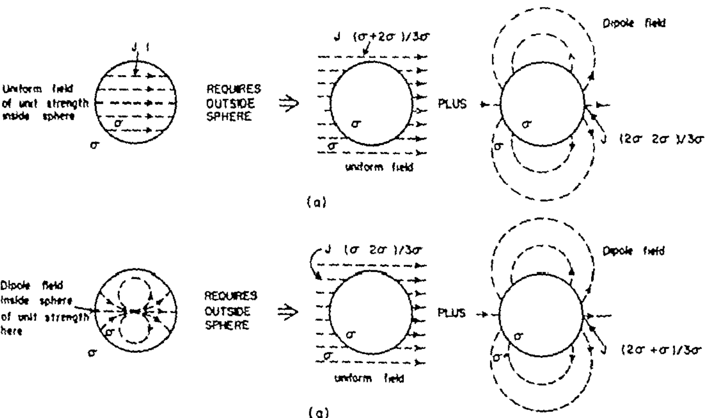


Fig. 6. Conversion of pure uniform and pure dipole fields inside sphere into uniform and dipole components outside. Note that the perpendicular component of current and the tangential component of the potential gradient are the same on both sides of the spherical interface.

just outside the spherical surface be multiplied by $(\sigma - \sigma)/3\sigma$ and the dipole component by $(2 + \sigma)/3\sigma$

These results may be combined in a single set of equations. If U and D are the strengths of the uniform and dipole fields just inside the surface and U and D their strengths just outside then

$$U = \frac{(\sigma + 2\sigma)}{3\sigma}U + \frac{(- \sigma)}{3\sigma}D \quad (5)$$

$$D = \frac{(2\sigma - 2\sigma)}{3\sigma}U + \frac{(2\sigma + \sigma)}{3\sigma}D$$

Fig 6 illustrates these equations.

We can apply these equations directly to our problem starting with a uniform field of strength $\vec{J}$ in the sphere of blood The field $\vec{J}_m$ in the muscle must be

$$\vec{J}_m = (+ 2\sigma_m 3\sigma)(\vec{u} J) +$$

$$(a, r)(2\sigma - 2\sigma_m 3\sigma)(\vec{u} \cos\theta + \quad (6)$$

$$\frac{1}{2}\vec{u} \sin\theta) J$$

The uniform component of the field on the other side of the second spherical surface is found from Eqs. (5) and (6) to be

$$\vec{J}_\infty = (\sigma_m + 2\sigma_L/3\sigma_m)(\sigma_b + 2\sigma_m 3\sigma)$$

$$(J_b\vec{u}) + (_m - _L/3\sigma_m)(a^b)\quad (7)$$

$$(2\sigma - 2\sigma_m/3\sigma_b)(J_b\vec{u})$$

We are not interested in the dipole component as it goes to zero as r goes to ∞. The terms of Eq (7) may be rearranged into the more convenient form

$$\vec{J}_\infty = \frac{1}{3} + \frac{2}{3} \quad + \frac{2}{9\sigma_L\sigma_m} \quad (8)$$

$$([a/b] - 1)(_m - \sigma_L)(- \sigma_m)(J u) \quad (8)$$

Note that since the dipole field in the lung vanishes as r becomes large we have shown that the initial assumption of a uniform field yields the correct field at infinity Thus it is *a* solution to our problem and therefore *the* solution

Note also that this procedure can be applied to arbitrarily many concentric spheres. In particular it can be used to show that there will be a uniform field within an inner isotropic homogeneous sphere surrounded by an anisotropic spherical shell (which can be considered to be formed by a great many shells of alternately high and low conductivity)

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Nature of intraventricular pressure differences induced by pharmacological agents in dogs*

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Piper Wiggers, and Hamilton and Brackett were among the earliest to note that the systolic pressure recorded from the apex of the left ventricle in normal dogs *at times* exceeded aortic systolic pressure Gregg and associates in 1937 suggested that such systolic pressure differences were due to the needle tip recording the high ventricular pressure being located partially in the left ventricular wall Subsequently Sauer[3] in 1950 reported the occurrence of a systolic pressure difference between the left ventricular apex and aorta in dogs in hemorrhagic shock.

More recent reports have located these systolic pressure differences within the left ventricle of the dog These intraventricular pressure differences induced in dogs by pharmacological and physiological interventions were considered due to muscular obstruction to left ventricular outflow [4] Such pressure differences were rare in normal anesthetized dogs[7] but occurred frequently in the presence of left ventricular hypertrophy [8] Pharmacologic agents having a positive inotropic action such as isoproterenol and norepinephrine enhanced these pressure differences[4,6] as did depletion of the circulating blood volume [5] These pressure differences were reduced or abolished by increasing resistance to ventricular ejection by partial aortic occlusion or administration of a vasoconstricting agent.[4] By 1963 and 1964 these intraventricular pressure differences in dogs, were being considered comparable to the intraventricular pressure differences encountered in patients with muscular obstruction to left ventricular outflow (muscular or hypertrophic subaortic stenosis hypertrophic obstructive cardiomyopathy)

However in 1963 and again in 1965

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Martin and co-workers[1] [?] demonstrated angiographically that in dogs in hemorrhagic shock the high ventricular pressure was found only at the apex of the left ventricle, an area that was devoid of angiographic dye in systole. Subsequently in 1965 Criley and associates[12] demonstrated by cineangiograms that when intraventricular pressure differences were recorded in normal dogs during isoproterenol infusion, the catheter recording the high intraventricular pressure was in fact entrapped by muscle at the cardiac apex following early and rapid emptying of the left ventricular cavity. These same authors[12] have also suggested that the intraventricular pressure differences noted in patients with muscular subaortic stenosis may not be due to obstruction to left ventricular outflow but rather to entrapment of the catheter recording the high intraventricular pressure by cardiac muscle.

Because of this controversy as to the nature and significance of intraventricular pressure differences in both animals and man we undertook studies both in dogs and in humans that we hoped would elucidate this problem. The present report deals with the nature and significance of pharmacologically induced pressure differences within the canine left ventricle as revealed by pressure recordings at multiple sites within this chamber.[14] Subsequent to the completion of these studies, Morrow and co-workers[13] have reported work indicating the nonobstructive nature of intraventricular pressure gradients in normal dogs. The techniques used were similar to those employed in the present study.

Methods

A chronic systolic overload of the left ventricle was produced in six mongrel dogs by creating a coarctation of the ascending aorta that narrowed the lumen to approximately one half or less of its original cross-sectional area.[4] Six months following this procedure the six dogs, ranging in weight from 10.8 to 19 Kg. were anesthetized in the supine position using pentobarbital 30 mg. per kilogram and ventilated with a Bennett respirator. The chest was opened through the fourth interspace bilaterally, transecting the sternum. After introducing a No. 7 Cournand catheter into the left ventricle via the left common carotid artery, pressure was recorded while withdrawing the catheter from the apex of the left ventricle to the aorta distal to the coarctation. The coarctation was then resected and the withdrawal pressure recordings were repeated. The same catheter was then positioned in the ascending aorta just distal to the aortic valve or in the left ventricular outflow tract (L.V.O.T.). A second No. 7 Cournand catheter of similar length was placed in the left ventricular inflow tract (L.V.I.T.) (that area of the left ventricle just inside the mitral valve) via the left atrial appendage and the mitral orifice. Catheters with and without side holds were used in this location. A shortened No. 7 Cournand catheter in which four side holes were created within 1 cm. of the tip was positioned 2 cm. within the left ventricular cavity at the apex (L.V. apex) via a stab incision through the apical dimple and sutured in place. The positioning of these catheters is depicted in Fig. 1. An uncalibrated 40 mm. flowmeter probe attached to a square wave electromagnetic flowmeter* was placed about the ascending aorta proximal to the repaired segment. The left external jugular vein was cannulated for administration of drugs by direct injection or constant infusion using a Harvard pump, and the right common femoral artery was cannulated for removal or administration of blood in heparinized 100 c.c. syringes. Pressures were recorded using two matched Sanborn transducers and a Sanborn multi-channel photographic recorder.

Experimental procedure

Effects of drugs. 1. After control observations, metaraminol (Aramine) was infused intravenously at the rate of 25 μg per minute into four dogs for a period of five minutes. This infusion was repeated in one animal following administration of phenoxybenzamine (Dibenzyline) 1 mg. per kilogram.

2. Norepinephrine 25 μg per minute was administered to all dogs for an interval determined by the appearance and magni-

*Carolina Medical Electronics, Inc.

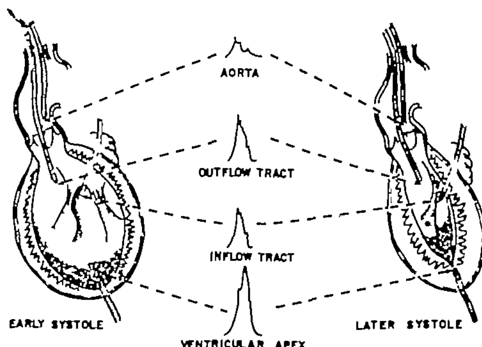


Fig. 1. Demonstrates (from top t bottom) the positioning of the three catheters to record (1) aortic or left en tricular outflow tract pressure (2) left entricular inflow tract pressure and (3) pressure at th apex of the left entricle during norepinephrine infusion The envisaged position of these catheters during early systole t which time ll ystolic pressures are equal is show t left. Later i systole (right) in the presence of an intra entricular pressure difference the pex catheter is en eloped or entrapped by muscle. The typical systolic pressures recorded i each of these area is shown i the center The show th location of the papillary muscle

tude of a pressure difference between the L.V apex and aorta. This drug stimulates both the α and β adrenergic receptors of the sympathetic nervous system[17] the former stimulation resulting in systemic vasoconstriction the latter having a posi tive inotropic action on the heart Believing that the pressure difference between L.V apex and aorta was the result of β-adrener gic stimulation and was opposed by α adrenergic stimulation the following pro- cedures were carried out to test this hypo- thesis. During norepinephrine infusion in three dogs the α adrenergic blocking agent phenoxybenzamine was administered in a dose of 1 mg per kilogram and the effect on the pressure difference assessed Follow ing a control period three animals received the β-adrenergic blocking agent propranolol (Inderal) 0 15 mg per kilogram intra venously and the norepinephrine infusion was restarted

*Supplied by Ayerst McKenna and Harrison, Montreal Canada.

Effects of decreased blood volume

During norepinephrine infusion (25 μg per minute) 200 c.c. of blood was rapidly removed from three animals.

Catheter manipulation

When a significant pressure difference between the L.V apex and the aorta was encountered during norepinephrine infu sion the following catheter manipulations were carried out to locate the site of the *intraventricular pressure* difference (1) the aortic catheter was advanced to the left ventricular apex until the pressure re- corded by this catheter was identical to that recorded by the L.V apex catheter Pressures were then continually recorded via both these catheters, while the aortic catheter was slowly withdrawn from the L.V apex to the aorta. (2) A similar L.V apex to aorta withdrawal pressure record ing was obtained while recording the pres- sure in the L.V I T (3) The catheter in the L.V I T was advanced to the ven tricular apex until the pressure it was re-

Table I. L.V. apex to aorta pressure differences following pharmacological and physiological intervention

	COA 15	COA 17	COA 19	COA 24	COA 25	COA 28
Control	0	0	38	0	0	0
Metaraminol 25 μg/min.	—	0	0	—	0	0
Norepinephrine 25 μg/min.	127	92	65	0	43	0
Norepinephrine 25 μg/min. Withdrawal of 200 c.c. of blood	—	—	—	90	131	16
Phenoxybenzamine 1 mg./Kg. Norepinephrine 25 μg/min	—	143	128	107		0
Phenoxybenzamine 1 mg./Kg. Metaraminol 25 μg/min.	—	55	—	—		—
Propranolol 0.15 mg./Kg. Norepinephrine 25 μg/min	0	0	0	—	—	—

COA, coarctation; L.V., left ventricular. All pressures recorded in mm. Hg.

cording equalled L.V. apex pressure. This L.V.I.T. catheter was then slowly withdrawn to the left atrium during pressure monitoring of this catheter and the L.V. apex catheter (4). A second withdrawal of the L.V.I.T. catheter from the L.V. apex to the left atrium was carried out while simultaneously recording L.V.O.T. or aortic pressure via the aortic catheter. At the end of each experiment the heart was opened to determine the exact position of the apical catheter.

Anatomical findings

After examining the internal aspect of the fresh heart, the specimen was placed in formalin and the fixed and cleaned ventricular myocardium was separated according to Herrmann's[4] method. The ventricular weights were then expressed as a ratio L.V./R.V. and compared with Herrmann's values for 200 normal dogs.[1]

Results

All withdrawal tracings from the L.V. apex to the distal aorta before relieving the aortic constriction failed to reveal a pressure difference either within the left ventricle or across the coarctation.

Table I shows the magnitude of the pressure differences encountered during control observations and following pharmacological and physiological intervention after the coarctation was relieved. A spontaneous pressure difference (38 mm. Hg) was found between the L.V. apex and the proximal aorta in only one animal.

Effects of drugs

1. Metaraminol, administered because of its action in releasing endogenous norepinephrine, failed to cause a pressure difference between L.V. apex and aorta in any of four dogs. Following administration of phenoxybenzamine 1 mg. per kilogram in one animal, a pressure difference of 55 mm. Hg appeared (Table I).

2. During the administration of norepinephrine 25 μg per minute in the six dogs, a pressure difference between L.V. apex and aorta, ranging between 43 and 127 mm. Hg was found in four (Table I). Phenoxybenzamine 1 mg. per kilogram given to four dogs during norepinephrine infusion caused a pressure difference to appear in one animal and augmented the pressure difference in two others, but failed to cause a pressure difference in the fourth (Table I). After injection of propranolol 0.15 mg. per kilogram, norepinephrine failed to elicit a pressure difference in the three animals tested. Fig. 2 shows pressure recordings from the aortic and L.V. apex catheters in one animal tested with the above drugs.

Effects of decreased blood volume

Withdrawal of 200 c.c. of blood during norepinephrine infusion caused the appearance of a L.V. apex to aortic pressure difference in the two dogs that failed to

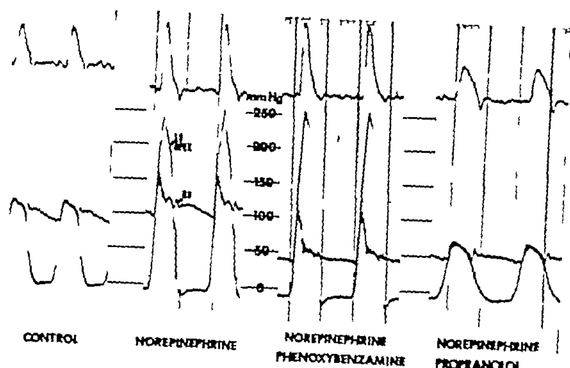


Fig 2 The upper tracing in each panel is the aortic flow curve recorded by an uncalibrated electromagnetic flowmeter In the lower part of each panel are shown simultaneous recordings of pressures from the left ventricular apex (LV apex) and aorta (A) in one animal (CON 17 Table I). The norepinephrine-induced LV apex to aorta systolic pressure difference was augmented following α-adrenergic blockade by phenoxybenzamine and abolished completely following β-adrenergic blockade by propranolol. In the presence of LV apex to aorta systolic pressure difference the aortic flow curve peaked in early systole suggesting exaggerated early systolic emptying of the left ventricle This flow pattern is different from the cut off flow curve with late systolic shoulder seen in human cases of muscular subaortic stenosis.[a,b]

develop a pressure difference with norepinephrine alone Venesection augmented a pre-existing pressure difference in one animal (Table I)

Catheter manipulation

Figs 3 4 and 5 depict representative findings of the catheter manipulation studies which were carried out to localize the site of the high intraventricular pressure and of the intraventricular pressure difference The results of these studies are depicted diagrammatically in Fig 1

In Fig 3 *A* the aortic catheter has been advanced to the LV apex where it recorded a high intraventricular pressure while the systolic pressure in the ventricular inflow tract (LV IT) was low On withdrawal of the aortic catheter to the LV OT (Fig 3 *B*) and aorta (Fig 3 *C*) the systolic pressure recorded by this catheter was identical to that recorded in the LV IT In Fig 4 (left) the catheter introduced through the mitral valve has been advanced to the LV apex where it recorded a high intraventricular pressure while the aortic catheter situated in the LV O T recorded a lower intraventricular pressure On withdrawal of the former catheter to the LV I T the intraventricular pressure difference disappeared and the LV I T and LV O T pressures were identical Fig 5 is similar to Fig 4 in all respects except that the aortic catheter was recording aortic rather than LV O T pressure On withdrawing the catheter from the LV apex to the LV I T, the pressure difference between the left ventricular apex and aorta disappeared Summarizing these findings (Fig 1) the high intraventricular pressure caused by norepinephrine infusion in dogs was found only at the LV apex. An intraventricular pressure difference existed between LV apex and LV I T as well as between LV apex and LV O T The LV I T and LV O T systolic pressures were always





Fig. 3. Infusion of norepinephrine 25 μg per minute. The aortic catheter has been advanced in retrograde fashion to the left ventricular apex (*L.V. apex*) where it records a high intraventricular pressure. The second catheter records L.V.I.T. pressure in all three panels. In Panel *A* there is an intraventricular pressure difference between L.V. apex and the L.V.I.T. In Panel *B* the aortic catheter has been withdrawn to the L.V.O.T., the intraventricular pressure in this location being precisely superimposed on L.V.I.T. pressure. In Panel *C* the aortic catheter has been withdrawn to the aorta where the systolic pressure is identical to that recorded in the L.V.I.T.

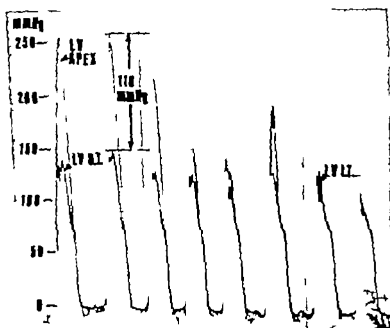


Fig. 4. Infusion of norepinephrine 25 μg per minute. On the left, the catheter introduced through the left atrium has been advanced to the apex of the left ventricle (*L.V. apex*) where it records a high intraventricular pressure and an intraventricular pressure difference exists between the pressure recorded by this catheter and the aortic catheter situated in the left ventricular outflow tract (*L.V.O.T.*). Withdrawing the former catheter to the left ventricular inflow tract (*L.V.I.T.*) the pressures in the L.V.I.T. and L.V.O.T. are identical. The pressure difference exists between the L.V. apex and both the L.V.O.T. and L.V.I.T.

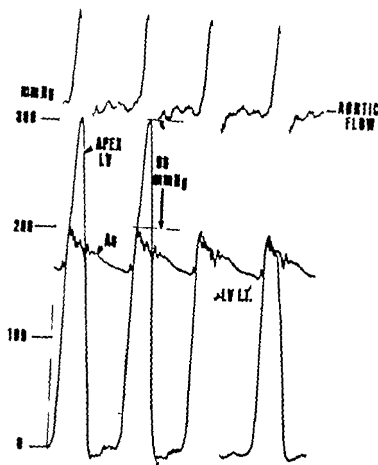


Fig 3 Infusion of norepinephrine 25 µg per minute On the left the high pressure at the L.V. apex is recorded by the catheter introduced via the mitral val. There is a systolic pressure difference between the L.V. apex and aorta. Withdrawing the intraventricular catheter from the L.V. apex to the L.V. I.T. there is no systolic pressure difference between the L.V. I.T. and aorta

equal to aortic systolic pressure as well as to each other

At times when a high intraventricular pressure was recorded at the L.V. apex the left ventricular pressure fell after the dicrotic notch in the aortic pressure (Fig 6 right) or after the simultaneously recorded L.V. O.T. or L.V. I.T. pressure

On opening the heart the L.V. apex catheter tip was found in the ventricular cavity within cm of the apex in all but one animal In the latter instance the tip was found in a subendocardial position at the base of a papillary muscle but communicating with the ventricular cavity via a small hole in the endocardium

The ascending aortic flow pattern invariably revealed a marked increase in velocity and volume of aortic flow in early systole in the presence of an intraventricular pressure difference (Fig 2)

Anatomical findings

Multiple ecchymoses were commonly seen on the endocardial surface of the L.V. The L.V./R.V. ratio averaged 1.879 (range 1.601 to 2.533) whereas Herrmann's mean figure was 1.398 ± 0.271 (providing evidence that the coarctation created in these dogs six months prior to these studies had resulted in a degree of left ventricular hypertrophy)

Discussion

The aim of this study was to produce intraventricular pressure differences in the canine left ventricle and to attempt to assess the significance of these pressure differences by the manipulation of heart

catheters within this chamber The coarctation was created six months prior to the time of study in order to produce left ventricular hypertrophy it having been previously demonstrated that with this type of preparation intraventricular pressure differences were more likely to occur than in a normal canine left ventricle.

The results of the catheter manipulation studies indicated that the high intraventricular systolic pressure was located only at the apex of the left ventricle, the systolic pressure in the left ventricular inflow tract being low and equal to the systolic pressure in the outflow tract and aorta. If these intraventricular pressure differences were the result of muscular obstruction in the left ventricular outflow tract, then the systolic pressure in all areas of the left ventricle proximal to the obstruction should be elevated including the left ventricular inflow tract pressure The fact that this latter pressure was not elevated has led us to conclude that the intraventricular pressure differences observed in these studies were not the result of muscular obstruction to left ventricular outflow

What then is the cause of the high intraventricular systolic pressure at the left ventricular apex? Gregg and associates[1] noted in 1937 that when a systolic pressure difference existed between the left ventricular apex and aorta of a normal dog blood could not be withdrawn in systole from the needle recording the high pressure. This observation suggested to these observers that the needle tip was not in the left ventricular cavity during systole but located in the wall of this chamber Martin and co-workers[11] provided cineangiographic evidence that the area of high systolic pressure at the apex of the left ventricle of dogs in hemorrhagic shock was devoid of radiopaque dye at the time the high systolic pressure was recorded More recently Criley and associates[13] have demonstrated that the heart catheter recording the high systolic pressure at the left ventricular apex in dogs during isoproterenol infusion was outside of the angiographic silhouette of the left ventricular cavity during systole These authors[1,13] have suggested that the elevated ventricular systolic pressures recorded by catheters in obliterated (emptied) areas of the left ventricle may be the result of sustained isometric contraction of this portion of the ventricle following evacuation of its blood content.

Morrow and co-workers[11] suggested that the elevated left ventricular systolic pressures recorded in the normal canine left ventricle, under conditions of decreased ventricular volume and positive inotropic stimulation of the heart were the result of the catheter tip being located in a muscular loculus isolated from the ventricular cavity and created by apposition of adjacent structures. At necropsy these authors noted that the catheter tip was frequently positioned in the recess between the posterolateral wall of the left ventricle and the anterior papillary muscle and suggested that the apposition of these structures may have created a loculus. Furthermore they were able to record identically elevated left ventricular systolic pressures from a catheter in such a recess and from a second catheter with both end and side holes in which the side holes were actually in the left ventricular wall These observations suggested that the elevated pressures reflected intramyocardial rather than intracavity pressure[14]

In the present study it was noted that, when a high pressure was being recorded at the left ventricular apex the decline in this high pressure not infrequently occurred after the dicrotic notch in the aortic pressure curve (Fig 6 right) This late decline in the elevated left ventricular systolic pressure occurred intermittently in the five animals in which the apical catheter was situated within the left ventricular cavity at postmortem as well as in the one animal in which the apical catheter was located in the subendocardial region of the anterior papillary muscle. This same phenomenon is evident in several of the pressure recordings published by Morrow and co-workers[11] Subendocardial intramyocardial tissue pressure has been reported to exceed intracavitary pressure[16,22] and to decline following the decline in intracavitary pressure[22] or following the dicrotic notch in aortic pressure.[22] The above observations suggest that the elevated ventricular systolic pressure recorded by a catheter partially located

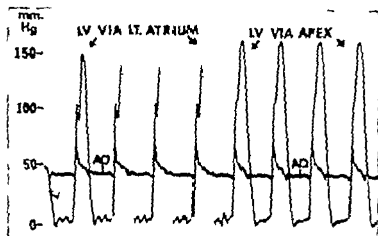


Fig. 6. Infusion of norepinephrine 25 μg per minute. The aortic pressure (AO) is a continuous recording. On the left the high left ventricular apex pressure is recorded via the catheter introduced via the left atrium and mitral valve (LV via lt. atrium). By switching a stopcock after the fourth heartbeat the high left ventricular apex pressure is recorded via the LV apex catheter (LV via apex). The latter pressure falls after the dicrotic notch in the aortic pressure, a characteristic noted in intramyocardial pressure recordings.[illegible]

within the ventricular wall[illegible] or enveloped by contracting cardiac muscle in an obliterated (emptied) portion of the ventricle reflects, to a variable degree, an elevated subendocardial intramyocardial tissue pressure. The elevation of this pressure may be physiological[illegible] or alternatively the intramyocardial tissue pressure in obliterated areas of the ventricle may exceed the intracavitary pressure elsewhere in this chamber by virtue of the Laplace relation (smaller radii of curvature in the emptied portions of the ventricle).

Early systolic evacuation of blood from the left ventricle, as evidenced by angiographic studies[illegible] and by the aortic flow pattern in the present study, appeared to be the mechanism by which the catheter recording the high intraventricular pressure became enveloped or entrapped by cardiac muscle. This view would be supported by the fact that manual emptying of the left ventricle by direct cardiac massage resulted in intraventricular pressure differences that were in all respects similar to those provoked by norepinephrine infusion.[illegible] Although in the present study the catheter recording the high intraventricular pressure was at the LV apex, equally elevated pressures may be recorded in other areas of the left ventricle when a catheter is so positioned near the wall that early systolic emptying of that area results in the catheter becoming enveloped or entrapped by cardiac muscle.[illegible]

In the present study, the high apical left ventricular systolic pressures were caused by a pharmacological agent (norepinephrine) having actions that would at the same time augment left ventricular emptying (β-adrenergic stimulation with positive inotropism) and decrease left ventricular emptying (α-adrenergic stimulation causing systemic vasoconstriction). The fact that blocking the latter action by phenoxybenzamine augmented pre-existing intraventricular pressure differences or resulted in the appearance of such pressure differences, is in keeping with the belief that augmented left ventricular emptying with subsequent catheter entrapment was the cause of the high apical systolic pressures. The fact that norepinephrine failed to elicit a high LV apex systolic pressure following β-adrenergic blockade implicates the stimulation of the cardiac β-receptors by norepinephrine as the cause of the augmented left ventricular emptying.

Although the nonobstructive nature of pharmacologically induced intraventricular pressure differences in dogs has previously been well demonstrated,[illegible] it is believed that the finding of a low systolic left ventricular inflow tract pressure under these circumstances provides a method for the

assessment of the nature of intraventricular pressure differences in man.[illegible] The finding of an elevated L.V.I.T. pressure in patients with muscular subaortic stenosis would strongly support the belief that obstruction to left ventricular outflow was the cause of the intraventricular pressure difference in these patients. On the other hand if the L.V.I.T. pressure were not elevated in patients with muscular subaortic stenosis this finding would support the suggestion that catheter entrapment by cardiac muscle was the cause of the intraventricular pressure difference as was the case in dogs. Assessment of the L.V.I.T. pressure in eight consecutive patients diagnosed clinically to have muscular subaortic stenosis has revealed that the L.V.I.T. pressure was elevated above L.V.O.T. and aortic pressure and equal to the pressure recorded at the L.V. apex, i.e. all intraventricular pressures proximal to the stenosis were elevated.[illegible] This finding is believed to provide strong evidence that there is obstruction to left ventricular outflow in muscular subaortic stenosis as well as providing evidence that there are two types of intraventricular pressure differences, i.e. due to outflow tract obstruction as in muscular subaortic stenosis and due to catheter entrapment or envelopment by cardiac muscle.[illegible]

Believing there are these two types of intraventricular pressure differences, it is of interest that norepinephrine abolishes the pressure difference in muscular subaortic stenosis,[illegible] whereas it causes the intraventricular pressure difference of catheter entrapment in dogs to appear. This difference in action of the drug is believed related to the fact that the vasoconstrictive action acts to relieve the muscular subaortic stenosis more than the positive inotropic action acts to accentuate the obstruction.[illegible] In catheter entrapment intraventricular pressure differences the positive inotropic action of norepinephrine predominates over the vasoconstrictive action.

Summary

Systolic intraventricular pressure differences were produced in six mongrel dogs by the intravenous infusion of norepinephrine six months following the surgical creation of an ascending aortic coarctation to produce left ventricular hypertrophy. The coarctation was removed prior to the described studies. These norepinephrine induced intraventricular pressure differences were accentuated by prior blood letting and following α-adrenergic blockade by phenoxybenzamine and were abolished by the β-adrenergic blocking agent propranolol. Manipulation of three intracardiac catheters revealed that the high intraventricular systolic pressure existed only at the apex of the left ventricle and that the systolic pressures in the left ventricular outflow tract, in the aorta, and in the left ventricular inflow tract were at all times equal and lower than the pressure at the left ventricular apex. If muscular obstruction to left ventricular outflow were the cause of these intraventricular pressure differences all pressures within the left ventricle proximal to the outflow obstruction should have been elevated including the left ventricular inflow tract pressure. The fact that the inflow tract pressure was not elevated is presented as evidence against the presence of outflow obstruction as the cause of these pressure differences. Evidence is presented to support the belief that the high systolic pressure at the left ventricular apex is the result of the catheter recording this pressure being enveloped, entrapped or imbedded in or by cardiac muscle due to exaggerated early systolic emptying of this portion of the left ventricle.

It is suggested that an assessment of left ventricular inflow tract pressure is essential in determining the nature of intraventricular pressure differences in man.

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The effects of calcium on isometric tension in isolated heart muscle during coupled pacing

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The fundamental role of calcium in the contraction of the heart has been appreciated for many years. Recent studies have shown that the ionized-calcium concentration in blood can be closely related to the contractile state of the intact myocardium.[1,2] Other more sophisticated studies have suggested that the entry and exit of calcium into and out of muscle cells serves as the basis for excitation-contraction coupling.[3] Coupled pacing or pair stimulation of heart muscle has been shown to produce great increases in the contractile force of intact and isolated heart preparations. Since this inotropic stimulus is one of the most powerful which has been observed, the effects on it of alterations in calcium were of interest. Accordingly, this study attempts to determine the effect of various calcium concentrations on the increased contractility produced by coupled pacing of isolated ventricular muscle strips.

Methods

Muscle strips measuring approximately 0.8 to 1.0 mm. by 10 mm. were taken from the right ventricle of adult male guinea pigs and prepared and mounted in a muscle chamber containing 50 ml. of Feigen's solution. Studies were performed at 37° C. and the bath was gassed with 99 per cent O_2 and 1 per cent CO_2. Isometric tension was recorded continuously with Statham GB-3-350 transducers after the muscles were stretched to produce maximal developed tension. This represented an increase of approximately 35 per cent over the resting length for each preparation. They were stimulated 60 times per minute through platinum plate electrodes with a Grass S-4 stimulator at supramaximal voltages approximately 50 per cent above threshold. A complete description of the techniques used in these experiments has been recently published.[4] After control measurements, coupled pacing was carried out with a variety of millisecond delays for the coupled stimulus in order to determine where the greatest enhancement of contractility occurred. These methods for coupled pacing have been described in detail.[5] After one hour in 2.6 mM per liter calcium for stabilization, calcium

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Table I. Effects of calcium on baseline developed tension

Calcium concentration (mM/L.)	No. of expt.	Developed tension mean ± S.E. (mg.)
2.6	18	208 ± 92
5.2	18	334 ± 88
10.4	17	440 ± 146
15.6	16	440 ± 106
20.8	16	388 ± 95

Table II. Effect of coupled pacing at various calcium concentration

Calcium concentration (mM/L.)	No. of expt.	Maximal developed tension Mean ± S.E. (mg.)
2.6	18	390 ± 118
5.2	18	593 ± 204
10.4	17	614 ± 116
15.6	16	548 ± 126
20.8	16	430 ± 88

chloride was added to produce concentrations of 5.2, 10.4, 15.6, and 20.8 mM per liter of calcium. A 2 per cent solution of calcium chloride was used for these additions. The result was a slight increase in osmolarity of less than 4 per cent at the highest calcium concentration. The developed baseline tension and that observed with coupled pacing was recorded at each level of calcium after a 15 minute period was allowed for equilibration. Control muscle strips prepared in this manner are stable for at least four hours. It was decided to carry out these experiments at normal body temperatures in order to ensure adequate ion transport during the short time allowed for equilibration for each level of calcium. The problem of hypoxia in the core of the muscle strip was recognized but the use of thin strips of muscle and short term experiments are considered to reduce this possibility. The long term stability of control preparations would tend to substantiate this view.

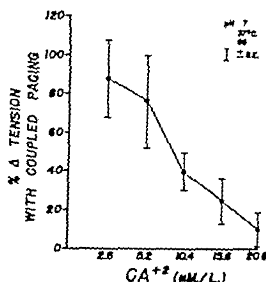


Fig. 1. The mean and standard errors for the percentage increase in developed tension with coupled pacing above the developed tensions occurring without coupled pacing at various calcium (CA^{++}) concentrations for 18 experiments.

Results

Effect of calcium alone. The addition of calcium to the solution bathing the muscle strips resulted in an increase in the developed tension at all concentrations (Table I). The maximum developed tension without coupled pacing was recorded at calcium concentrations of 10.5 and 15.6 mM per liter. At a higher calcium concentration (20.8 mM per liter) and two lower calcium concentrations (2.6 and 5.2 mM per liter) the developed tension was lower (Table I).

Effects of coupled pacing. Coupled pacing increased the developed tension in all preparations studied at normal calcium concentrations. The greatest isometric tension recorded during coupled pacing was at 5.2 and 10.4 mM per liter calcium (Table II), but the greatest percentage increase over the control level of tension was recorded at 2.6 mM per liter calcium (Fig. 1). At all concentrations of calcium above this value coupled pacing resulted in a smaller increment in developed tension until at 20.8 mM per liter calcium concentration there was no consistent increase in developed tension (Fig. 1). During coupled pacing the interval between the basic stimulus and the coupled stimulus

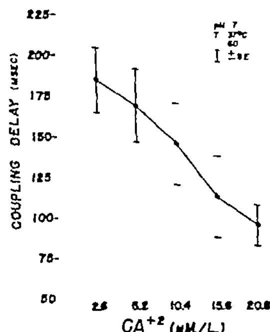


Fig. 2. The mean and standard errors of the interval between the basic stimulus and the coupled stimulus necessary to produce maximal developed tension during coupled pacing at various calcium concentrations.

necessary to produce maximal developed tension became progressively shorter at higher calcium levels (Fig. 2).

Discussion

Recently it has been suggested that excitation-concentration coupling of muscle results when electrical impulses traveling along the transverse tubules (T system) release calcium from the lateral cisternae of the endoplasmic reticulum. This calcium diffuses to the contractile filaments, initiates contraction and may even control the force of the contraction. The reaccumulation of calcium in the sarcoplasmic reticulum results in relaxation.[13] Although these studies have been carried out primarily in skeletal muscle, they probably apply to cardiac muscle too. It thus seems possible that the enhanced contractility produced by coupled pacing of cardiac muscle may result from a greater quantity of calcium reaching the contractile machinery with each depolarization due either to an alteration of the mechanism returning calcium to the sarcoplasmic reticulum or to a larger quantity of calcium entering with each depolarization. These studies were carried out to demonstrate that the concentration of calcium bathing the muscle does affect the increase in contractility produced by coupled pacing. This enhancement appeared to be greater at normal calcium concentration and was not consistently present at very high concentrations. Although these studies were carried out at normal mammalian temperatures, the use of thin strips of muscle and short term experiments were thought to reduce the tendency for the development of hypoxia of the central core of muscle. This is supported by the stability of control muscles for four hours. It thus appears that the concentration of calcium is directly related to the increase in contractility produced by coupled pacing and that a maximum is reached at normal calcium concentrations. It is interesting to speculate that the increase in developed tension observed without coupled pacing resulted from a larger quantity of calcium at the site of the intracellular contractile machinery and that coupled pacing cannot further enhance this at very high calcium concentrations (Table II). The precise relationship of calcium fluxes to altered contractility during coupled pacing, however, has not been elucidated.

Since the enhanced contractility of coupled pacing is a modification of postextrasystolic potentiation, these findings are in agreement with Hoffman and co-workers[11] and Nayler[12] who both noted that high calcium concentrations abolished or decreased the postextrasystolic potentiation. These investigators did not investigate calcium concentrations as high as those used in the present study because solutions containing higher concentrations of bicarbonate may result in the precipitation of calcium salts. Other studies using lowered calcium concentrations have failed to show changes in augmentation produced by extra contraction.

The delay after initial depolarization for the second impulse during coupled pacing to produce maximal enhancement of contractility progressively shortened with increasing calcium concentrations; this suggests earlier repolarization of the myocardium at higher calcium levels.

Summary

The effects of calcium concentration on the positive inotropic effects of coupled pacing were studied in a myograph An increase in calcium concentrations in the muscle bath up to levels of 15 6 mM per liter resulted in the development of greater isometric tension in guinea pig ventricular strips, but the increment n tension produced by coupled pacing fell progressively at all calcium concentrations above 2 6 mM per liter The delay between the basic stimulus and the coupled stimulus to produce maximal enhancement of contractility during coupled pacing decreased progressively with higher concentrations of calcium

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Tachycardias with alternation of the ventricular complexes

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Tachycardias with alternating ventricular complexes which may be bidirectional in some leads have always created considerable interest. Usually a complication of digitalis therapy, the tachycardias imply a poor diagnosis and are often terminal. Treatment requires immediate correction and continuous supervision. The mechanism of their origin, however, remains controversial.

Two main types of alternating tachycardias are differentiated. In one the form of the ventricular complexes alternates during a regular rhythm. In the other the duration of successive cycles also alternates. Two possible mechanisms to explain alternation were considered initially. The first postulated that impulses from two active centers spread alternately over the ventricles. The second proposed that impulses from one center were conducted alternately over the ventricles. The latter seemed probable in cases associated with regular rhythm. Indeed, the theory advanced by Luten[7] that one center can induce alternation by disturbance of intraventricular conduction has been proved. Although the single-center hypothesis has been declared improbable in the presence of an irregular rhythm, experiments demonstrate its validity. Even when one center fires off impulses, an alternation of rhythm, i.e., a longer cycle alternating with a shorter one, can be observed.[10,11] Other explanations for the mechanisms of alternation apply the concept of parasystole or reentry.

In the following pages, experimental and clinical tracings will be described which help to elucidate the nature of tachycardias with alternating forms of the ventricular complexes. They demonstrate that several totally different mechanisms may be responsible for identical electrocardiograms.

Experimental observations

An early explanation of the alternating tachycardias assumed the presence of two ventricular centers which would activate the ventricles alternately. The theory seemed improbable because a fast center would suppress the slow center unless both were protected by an entrance block. Fig. 1 demonstrates such a double parasystole with two simultaneously active centers producing a tachycardia with alternating ventricular complexes.

The tachycardia in Fig. 1 resulted after 0.05 ml. of a 20 per cent solution of sodium chloride was injected subepicardially in the right and left ventricles of a dog's

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Fig. 1, A–C. Tachycardia with alternating ventricular complexes induced by the presence of two ventricular centers. Dog experiment; the heart exposed. Lead II. Hypertonic sodium chloride solution was applied focally on the right and left ventricles. At the beginning of *A* a right ventricular tachycardia appears induced by focal administration of hypertonic saline. In the second half of *A*, in *B*, and at the beginning of *C* alternation is present. In the second half of *C* a left ventricular center takes over.

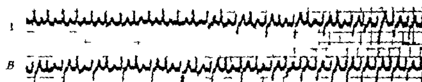


Fig. 2, A, B. Experimental alternating tachycardia induced by injection of hypertonic saline into the A-V node and epinephrine, given intravenously. Dog experiment, Lead II. The atria fibrillated because of focal application of aconitine. Injection of a hypertonic solution of sodium chloride into the A-V node created an A-V junctional tachycardia. The rate increased when 0.2 ml. of a 1:1000 solution of epinephrine was injected intravenously and alternation appeared.

heart during pentobarbital anesthesia. Hypertonic saline, which induces rapid firing of impulses when applied focally to a nerve, also provokes a ventricular tachycardia when applied similarly to a dog's ventricle. Not only do these tachycardias last several minutes, but the firing focus is protected from the sinus or other impulses spreading over the heart.[11] The center of impulse formation is protected by its rapid rate which prevents depolarization by other impulses.

In the experiment from which Fig. 1 was obtained, a right ventricular tachycardia appeared immediately after the subepicardial injections with a rate of 214 (cycle length 0.28 second). The tracing (Lead II) has been cut into 3 strips to facilitate reproduction. An alternation of QRS complexes follows in the second half of Fig. 1, *A* which, persisting in Fig. 1, *B*, changes gradually into a left ventricular tachycardia with a rate of 186 in Fig. 1, *C*. We may assume that at first (beginning of Fig. 1, *A*) the right ventricular center is faster. Later the two centers are obviously firing with approximately the same rate. When the rate of the right ventricular center slows, the left ventricular center jumps in. As would be expected, the slight variation of the form of the QRS during the alternation results whenever the cycle length of either center varies by a few thousandths of a second.

This tracing demonstrates clearly that a ventricular tachycardia with alternation of the form of the QRS complexes is possible when two centers function simultaneously and independently.

The tachycardia recorded in Fig. 2 followed the injection of a 20 per cent solution of sodium chloride into the A-V node 30 minutes after focal application of aconitine to the right atrium had induced atrial fibrillation. In spite of the rapid ventricular rate irregular fibrillation waves are visible. Shortly before Fig. 2, *A* was obtained, 0.2 ml. of 1:1000 epinephrine was injected intravenously. As the rate of the A-V tachycardia increased to 230, an alternation of the QRS complexes appeared (Fig. 2, *A* and *B* are continuous). The end of Fig. 2, *A* exhibits an extrasystole. In the second half of Fig. 2, *B* the ventricular complexes which at first appear alternately persist

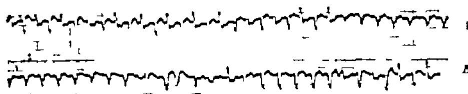


Fig 3 A B Alternating A V nodal tachycardia with disappearance of alternation when carotid sinus pressure slowed the rate. An alternating digitalis-induced tachycardia (Lead II) is abolished when the rate was slowed by carotid sinus pressure A few seconds after the end of the pressure (its duration is approximately suggested by the horizontal black line) the alternation re-appeared (B) A and B were continuous.



Fig 4 A C Carotid sinus pressure abolishes alternation in an A V junctional tachycardia without change of rate. Lead II shows digitalis-induced tachycardia with alternation which disappears during carotid sinus pressure. At the end of C the form of the ventricular complexes suddenly changes spontaneously The rate remains the same throughout the tracings.

This tracing demonstrates how activity in a single center leads to an alternating A V junctional tachycardia when every second beat is aberrantly conducted Although the rate remained unchanged save for the slight variations expected in an experimental tachycardia the alternation disappeared when all complexes were aberrantly conducted.

Clinical observations

Fig 3 shows in Lead II a typical tachycardia with alternating complexes in a patient with atrial fibrillation receiving digitalis. The alternating tachycardia with a rate of 196 was abolished by carotid sinus pressure when the rate slowed to 150. During carotid sinus pressure, QRS complexes appeared without a pause in regular succession bearing a form that was similar but not identical to one of the complexes seen during alternation. A few seconds after the carotid sinus pressure (indicated approximately by the black signal line) the alternation reappeared preceded by single beats showing the same form as those during alternation This result could be obtained repeatedly as long as the tachycardia lasted

This tracing represents an A V junctional tachycardia due to digitalis with alternation of the intraventricular conduction which repeatedly disappeared when the rate slowed

Fig 4 presents three strips in Lead II obtained from a 56-year-old patient with coronary sclerosis and congestive heart failure who received 0 25 mg of digoxin 4 times daily for two weeks. These tracings were originally continuous, but three ventricular complexes were removed between B and C of Fig 4 In Fig 4 A QRS complexes with a deep S wave alternate with those having a high R wave Next two ventricular complexes with deep S waves follow in succession before another complex with a high R occurs. After two such groups, alternation resumes. During and for several seconds after carotid sinus pressure the complexes with the deep S waves disappear Suddenly at the end of Fig 4 C they reappear to persist without apparent

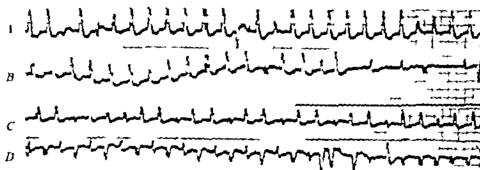


Fig 5 A-D A-V junctional tachycardia stopped temporarily by carotid sinus pressure. A shows (Lead II) regular tachycardia interrupted by ventricular extrasystoles which appeared in digitalized patient who had atrial fibrillation. B shows the sudden disappearance of the tachycardia during carotid sinus pressure. Half an hour later (C) regular tachycardia again appeared with abnormal intraventricular conduction of every third beat. Shortly afterwards alternation is again visible (Lead III) and it was transformed by carotid sinus pressure into regular tachycardia (D).

reason The QRS complexes throughout the tracing are 0.08 second wide and the diagnosis of an A-V junctional tachycardia seems justified.

In this observation the disappearance of alternation by carotid sinus pressure cannot be explained by reduction of rate which remains between 125 and 122 (cycle lengths between 0.48 and 0.49 second). Obtained repeatedly this effect of carotid sinus pressure was certainly not a coincidence. If the QRS complexes with the high R wave are conducted normally and those with the deep S waves aberrantly then the disappearance of the latter on carotid sinus pressure could be explained by the improvement of intraventricular conduction which results when through carotid sinus pressure acetylcholine releases norepinephrine. Another possibility would be that carotid sinus pressure alters intraventricular conduction because of its effect on the activation of the A-V node. Finally at the end of Fig 4 C fatigue again sets in so that not only every second or third but each beat is abnormally conducted.

The phenomenon that alternation involves group of beats and not successive beats has been called group alternans.

Fig 5 was registered from a 62 year-old man with hemiparesis and aphasia. Atrial fibrillation with a rapid ventricular rate has been treated with 1 mg of digoxin intravenously and 0.5 mg intramuscularly. The patient died four days after admission.

Fig 5 A (Lead II) shows a regular tachycardia with a rate of 142 interrupted by extrasystoles. In Fig 5 B (Lead II a few hours later) carotid sinus pressure stopped the tachycardia, disclosing atrial fibrillation and ventricular complexes of varying configuration. This tachycardia which manifests QRS complexes differing from those conducted from the atria, could be interpreted as a ventricular tachycardia. Response of a ventricular tachycardia to carotid sinus pressure is however rare. In view of the effect of carotid sinus pressure a more plausible explanation would be an A-V junctional tachycardia with aberrant ventricular complexes.

In Fig 5 C (Lead aVL) taken half an hour later a regular tachycardia of 136 is re-established but with every third beat aberrantly conducted. Alternation of the form of the ventricular complexes follows in Fig 5 D (Lead III) when the rate increased to 166. Slowing the rate to 136 by carotid sinus pressure abolished the alternation.

These tracings show an abnormal A-V junctional rhythm exhibiting alternation which disappears when carotid sinus pressure slows the rate. This observation also demonstrates that a digitalis-induced A-V junctional tachycardia may respond to carotid sinus pressure in two ways. It may be slowed or it may be stopped completely.

Fig 6 shows the three standard leads recorded from a 65-year-old man with

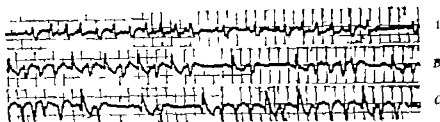


Fig. 6. *A–C.* Interpolated extrasystoles imitate ventricular tachycardia with alternating ventricular complexes. The three standard leads show right bundle branch block in a patient with sinus rhythm and ventricular extrasystoles, most of which are interpolated.

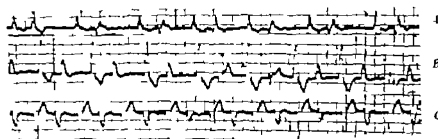


Fig. 7. *A–C.* The appearance of an A-V junctional rhythm with increasing rate in a patient with bigeminal rhythm gives the impression of ventricular tachycardia with alternation of form and rhythm. The three leads represent Leads aVR, aVL, and aVF. In a patient with atrial fibrillation ventricular bigeminy had appeared during digitalis therapy. When the rate of the basic rhythm (A-V junctional rhythm) to which the extrasystoles were coupled increased (Leads aVL and aVF), a tachycardia with alternation of form and rhythm is suggested.

coronary sclerosis. In the center of Lead II after a long pause a sinus beat with a right bundle branch block pattern and a P-R interval of 0.18 is followed by a ventricular extrasystole displaying a blocked sinus P wave in the T wave. Throughout the tracing P waves appear at intervals of 0.66, 0.68, 0.70, 0.70, and 0.69 second. At the beginning of Lead II identical ventricular extrasystoles follow a sinus beat and then an aberrantly conducted sinus beat. A less likely interpretation would be a sinus beat followed by a series of ventricular extrasystoles. Next, interpolated ventricular extrasystoles simulate a ventricular tachycardia with alternation of the form of the ventricular complexes. Similar disturbances of rhythm appear in the other leads. In the second half of Lead II two ventricular extrasystoles occur in succession. It is not rare that a sinus beat after an interpolated ventricular extrasystole assumes the form of the extrasystole, because the myocardium surrounding the site of origin of the extrasystole being first activated recovers first and responds readily to the following sinus impulse.

These tracings show that interpolated ventricular extrasystoles can simulate the pattern of a tachycardia with alternating ventricular complexes.

In Fig. 7, Leads aVR, aVL, and aVF were recorded from a 68-year-old woman with coronary sclerosis and heart failure who was given 0.75 mg. digoxin on admission and 0.5 mg. every 8 hours for three doses in spite of having received at home 0.25 mg. of digoxin and 500 mg. of chlorothiazide daily for several months. Lead aVR shows atrial fibrillation, intraventricular block, a marked digitalis effect in the conducted beats, and ventricular bigeminy with variform ventricular extrasystoles. The rate of the basic rhythm gradually increases in Leads aVL and aVF. With increasing rate and consequent shortening of the postextrasystolic pauses in aVF a regular alternation appears having the following intervals measured in hundredths of a second: 48, 44, 48, 44, 48, 44, 52, 43, 48, 43, 49, etc.

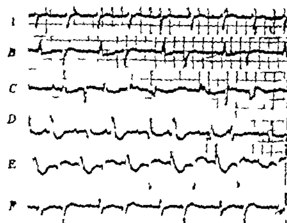


Fig. 8. *A-F*. A fast A-V junctional rhythm in a patient with ventricular bigeminy evokes the pattern of ventricular tachycardia with alternation of the ventricular complexes. Leads I, II, III, V2, V3, and V5 are reproduced. This patient had a P-R interval of 0.21 second and multiform ventricular extrasystoles appeared (Lead II). Multiform extrasystoles are seen in Lead III following each other without sinus beats. An alternating tachycardia appeared while Lead V3 was registered and a simple ventricular bigeminal rhythm was seen again in Lead V5.

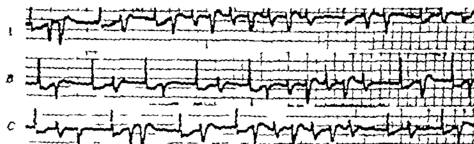


Fig. 9. *A-C*. When ventricular extrasystoles with different complexes and different coupling follow each other the pattern of ventricular tachycardia with alternation of form and rhythm appears. *A* and *C* represent Lead II, *B* is Lead III. The tracings (particularly the first half of (*B*) show that in this patient with atrial fibrillation two forms of ventricular extrasystoles with a different duration of the coupling appear. In all three leads for short stretches these two forms of extrasystoles follow each other directly, leading to a ventricular tachycardia with alternation of form and rhythm.

This tracing demonstrates how a simple bigeminal rhythm assumes the guise of a tachycardia with alternation of the form of the ventricular complexes when an A-V junctional rhythm develops an increased rate.

Similar changes were observed while Leads I, II, III, V2, V3, and V5 of Fig. 8 were being recorded in a 60-year-old woman with coronary sclerosis who received an unknown quantity of digitalis prior to admission. In Lead I the P-R interval is prolonged to 0.21 second. Lead II disclosed a bigeminal rhythm with multiform ventricular extrasystoles. In Lead III a series of multiform ventricular extrasystoles follow a sinus beat or ectopic beats. A regular bigeminy in V2 (Fig. 7, *D*) assumes the appearance of a tachycardia with alternating forms of the ventricular complexes in V3 (Fig. 7, *E*) when a rapid A-V junctional rhythm causes A-V dissociation. Successive intervals measure 54, 46, 54, 52, 48, 47, 46, 48, etc. A simple bigeminal rhythm reappears in V5.

Fig. 8, like Fig. 7, shows how a bigeminy without undergoing changes simulates a tachycardia with alternation of form and cycle length when a rapid A-V rhythm intervenes.

Fig. 9 was taken from a 74-year-old woman with coronary sclerosis and atrial

fibrillation who had received an unknown quantity of digitalis. Every conducted beat is followed by one or two extrasystoles. In Fig. 9,*B* (Lead III) two forms of extrasystoles follow the first four conducted beats. One with the deep S wave has a coupling of 37. The other with a R wave has a coupling of 46. For a brief interval a tachycardia with alternating ventricular complexes appears in each lead. In Fig. 9,*A* (Lead II) where the pauses preceding the extra beats with the deep S are shorter than those preceding the extrasystoles with the high R wave, the successive intervals during alternation are 34, 46, 38, 44, 39, 42, 39, 43.

Clearly in this tracing two ventricular foci of extrasystoles operate which transmit impulses alternately to the heart.

Discussion

For many years tachycardias with alternating ventricular complexes were considered to be ventricular tachycardias. The experimental and clinical observations described above support the evidence adduced by various investigators that alternation is not always ventricular in origin. It has been demonstrated that alternation of the ventricular complexes can be seen in supraventricular rhythms.

A considerable advance was achieved when it was found that carotid sinus pressure[19,21] or the Valsalva experiment can stop these tachycardias immediately. This evidence rendered the diagnosis of a ventricular tachycardia improbable. That tachycardias with alternation of cycle length are stopped or slowed by carotid sinus pressure[1,20,21] indicated that these tachycardias may result from firing in one center. In fact, carotid sinus pressure helps to determine whether an alternating tachycardia derived from one or two centers. When carotid sinus pressure or, in the experiment, faradic vagus stimulation arrests both forms of abnormal ventricular complexes of an alternating tachycardia, the diagnosis is safely inferred to be an A-V junctional tachycardia with alternation. On the other hand, when carotid sinus pressure suppresses only one form of the ventricular complexes while the other persists in form of extrasystoles, the diagnosis must presuppose activity of a supraventricular center and ventricular extrasystoles.[21]

A ventricular origin of an alternating tachycardia must be questioned whenever the width of the alternating complexes is noted, as in Figs. 3 and 4, to be only 0.08 to 0.09 second. This observation speaks for aberrant conduction.

While the site of origin of an alternating tachycardia may be supraventricular or ventricular, certain other features which have been described in the tracings above or in the literature warrant review. All previously considered mechanisms actually exist; only re-entry has not yet been demonstrated. Alternation may occur in rapid atrial rhythms in the presence of intraventricular conduction disturbances. This has been seen experimentally[4,19] particularly after epinephrine[4] or during an atrial tachycardia with right bundle branch damage.[19] As illustrated in Figs. 2, 3, and 4, a regular fast A-V junctional rhythm, usually the consequence of digitalis therapy, may lead to aberrant conduction of each or every second or third QRS complex. An A-V junctional tachycardia which appears in a digitalized patient who develops a ventricular bigeminy may, as the rate increases, evolve into an alternating tachycardia (Figs. 7 and 8). Such an increase in rate may be gradual or paroxysmal lasting for a few seconds or days. Another mechanism producing alternation is a ventricular tachycardia due to activity in one center[3] (perhaps our Fig. 5) or in two centers, which are mutually protected by their rapid rates (Fig. 1). Extrasystoles from different centers may follow each other in alternation (Fig. 9) or, if interpolated, simulate an alternating tachycardia (Fig. 6). Throughout our observations, alternation occurred in a variety of rhythms including sinus rhythm, regular A-V junctional rhythm, or atrial fibrillation.

In our observations (Figs. 1 to 5) and those of others an alternating tachycardia changes into a tachycardia with a constant form of QRS complexes. In these instances, either each beat becomes aberrantly conducted instead of alternate beats or aberration disappears. Aberration disappears when procaine amide slows the rate[1] and resumes when the rate increases.[4,5]

It now seems certain that an alternation of cycle length can be observed even in the presence of *one* impulse-forming center. An alternation of cycle length amounting to a few hundredths of a second with constant form of the ventricular complexes is often encountered in clinical and experimental tachycardias, especially those with higher rate. A greater alternation of cycle length is frequently observed when a ventricular tachycardia results from the focal application of a hypertonic solution of sodium chloride or sodium oxalate or sodium citrate on ventricles of the exposed dog heart. Warming the area of application increases the rate of the tachycardia, proving that impulses are fired off at this site. Explanation of this phenomenon is not easy; it is probable that the rate of impulse formation in the center is much higher and a 3:2 block (similar to the Wenckebach phenomenon) creates an alternation of cycle length. When the QRS complexes are widened, alternation of cycle length often occurs in one lead only, in which the beginning or end of the QRS is isoelectric due to a zero potential caused by summation of vectors. The ventricular complex appears to start later or end earlier than the actual onset or end of ventricular depolarization.

Of interest and not fully explained is the disappearance of alternation during carotid sinus pressure without slowing of the rate (Fig. 4).

Summary

Alternating tachycardias with regular or varying cycle lengths may result from stimulus formation in one or two centers. This was established by both experimental and clinical observations.

Experimentally, rapid impulse formation may evoke an alternating tachycardia from two ventricular centers as in a double parasystole or from a single focus in the A-V node. Clinically, alternation could be abolished by carotid sinus pressure with or without slowing, be simulated by interpolated ventricular extrasystoles, be recorded with an increase in A-V nodal rate in patients with bigeminy, and be caused by extrasystoles with different couplings and different forms.

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Case reports

Dissecting aneurysm distal to coarctation of the aorta with long survival

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The adult type of coarctation of the aorta if severe is seldom seen in the older age groups and is rarely associated with healed dissecting aneurysm Reifenstein Levine and Gross reviewed 104 autopsy cases of the adult type of coarctation which occurs as a focal area of constriction usually 1 cm or less in length most frequently at or just below (but rarely above) the insertion of the ligamentum arteriosum. They found that its incidence was one per 3 000 or 4,000 autopsies and that it was not usually associated with other major congenital anomalies. The condition is five times more common in male patients than in female. The mean age at death is 35 years Abbott's[2] earlier series of 200 cases of adult type coarctation agrees fairly closely with these findings. Age at death has been reported from 6 months to 9 years. Longevity depends upon the severity of the aortic constriction the adequacy of collateral circulation, and the development of complications. In the series of Reifenstein Levine and Gross, 74 per cent died as a result of complications attributable to coarctation while 26 per cent died of incidental unrelated causes. The common complications resulting in death are congestive heart failure rupture of the aorta bacterial endocarditis or aortitis, and rupture of an intracranial aneurysm Rupture of the aorta is a common cause of death and may occur with or without aneurysm formation. The site of rupture is most often proximal to the constriction The oldest recorded case of dissecting aneurysm distal to an aortic coarctation occurred in a 62 year-old man who died of self inflicted gunshot wounds 12 days after the onset of his painful condition.

This report describes the oldest patient with an aortic dissection distal to the coarctation with the longest survival after dissection. The clinical diagnosis was made 25 years prior to autopsy confirmation Cardiomegaly developed only late in the clinical course

Case reports

A 65-year-old business executive was admitted to the Peter Bent Brigham Hospital for the fifth and final time with dyspnea and edema.

In childhood he had reduced exercise tolerance. Beginning at age 15 he had frontal headaches and nausea A systolic murmur and hypertension were noted at 18 years of age At age 40 he was seized by

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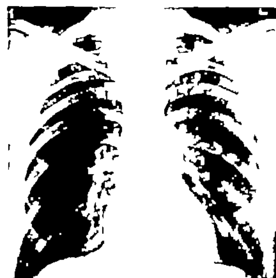


Fig. 1 Chest film taken t 45 y ar of age show prominent aortic nob and shadow of the aneurysm just below. Heart size as 11 per cent greater than anticipated from transverse diameter measurements. Notching of the pper ribs is seen, particularly on the right. A second examination 5 years later re- vealed no change.



Fig. 2 Chest film t the ge of 64 years reveals a marked increase in heart size due t left entricula hypertrophy. Pulmonary ascular markings are increased.

excruciating pain the lower back while playing cards. This was accompanied by slight terior chest pain ithout radiation. H recalled perspiring profusely nd feeling extremel weak. The symptoms lasted 10 to 12 hours and disappeared. There was no loss of consciousness and his blood pressure was maintained. Electrocardiograms were normal. His first admission to the Peter Bent Brigham Hospital as t age 45 years, th bleeding duodenal ulcer. The heart as of normal size and A was louder tha P. There was grade 2 systolic m rmur heard maximally in the first nd second left sternal border I terspaces nd lso heard 6 cm t the left of the sternal margi over both carotids, and over the upper thora Femor l pulses were deficit nd ym metrical. The blood pressure in the right arm w 138/56 nd in the right leg as 96/76 mm Hg. A chest film revealed loc lized dilatation of the descending aorta that began 3.5 cm below the top of th arch, extended t the left and decreased toward the diaphragm (Fig. 1). The lungs were clear d the heart was not enlarged. There were concav notches on the lower borders of the ribs, more marked on the right. Fluoroscopy demonstrated a normal expansion of the aortic arch but barely per ceptible pulsations of the dilated orta. A standard lead ECG showed left is deviation. The linical diagnosis was coarctation of the aorta with healed dissecting neurysm distal t the constriction. Bleeding from the du lenal lcer w ntrolled medically.

The second admission 5 y ar later w f r tre t ment of recurrent abdominal pain. H lso com plained of occasional palpit tions and mild hortness of breath on exertion. The arm blood pressure w



Fig. 3 Oblique iew lso t the age of 61 y rs re- veals displacement of the barium-filled esophagus by the aortic arch. J st below is the fusiform shadow of the aneurysm with a sharply defined border of lcific tion. The area of coarctation is proximal t th aneurysm.

148/85 mm Hg. The chest film nd ECG ere l normal.

H as admitted for the third time 14 y la er t the age of 64 years, w th wheezing respiration. There as slight lubbing of the fi gers. Hi blood



Fig. 4. Anterior view of the heart and aorta opened longitudinally through the site of coarctation. The pin beneath the ruler is inserted posterior to the ligamentum arteriosum. An atheromatous plaque on the intimal surface between the end of the ruler and the coarctation denotes the aortic end of the ligamentum arteriosum. From this site the membranous reflection of the coarctation extends across the lumen. Another pin is inserted through the ostium of dilated intercostal artery into the dissecting aneurysm which lies posterior to the aorta.

pressure was 160/62 mm. Hg. A grade 2 diastolic murmur was heard at the base of the heart, as well as the systolic murmur previously noted and a gallop rhythm. The ECG showed left ventricular hypertrophy and conduction defect. The QRS interval was 0.12 seconds. Chest film showed left ventricular enlargement and calcification on the border of the previously demonstrated aneurysm in the region of the descending aorta (Figs. 2 and 3). He was discharged on digitalis and diuretics.

The patient was readmitted at the age of 65 years because of increasing dyspnea. He had gallop rhythm, pulsus alternans, and left pleural effusion which was tapped twice. He improved and was discharged but had to be readmitted six weeks later because of progressive dyspnea and edema. He had bilateral pleural effusions and did not respond to vigorous heart-failure therapy. He became comatose and died on the sixth hospital day.

Postmortem examination. The pertinent positive findings included ankle and pedal edema, bilateral osteoarthropathy, pleural and pericardial effusions, and ascites. The heart was dilated and hypertrophied. It weighed 680 grams. The left and right ventricular walls measured 2.0 cm. and 0.6 cm. in thickness respectively. There were microscopic foci of fibrosis in the left ventricular wall. The aortic ring was dilated with a circumference of 9.3 cm. The coronary arteries were patent, with minimal atherosclerosis. The foramen ovale was covered by oval membrane, but a small probe could be passed obliquely from the left to the right atrium. The proximal aorta and its three major branches were markedly dilated, hypertrophied, and diffusely involved by large and small, ovoid, yellow atheromata. Just distal to the ligamentum arteriosum there was severe narrowing of the aorta, which measured 1.8 cm. in circumference. A small, membranous, pliable and smooth flap of tissue projected from the posterior wall of the coarctation into the lumen at the area of greatest narrowing (Fig. 4). There was no evidence of aortitis. A large dissecting aneurysm extended from its apparent origin in an intercostal artery 3.5 cm. distal to the coarctation, to within 3 cm. of the level of the diaphragm, where it reentered the aorta. The dissection did not extend proximal to the coarctation. The aneurysm measured 4.8 cm. in greatest diameter. The lumen of the false channel was completely occluded by concentrically laminated thrombus with calcification (Fig. 5). Proximal to the coarctation there was severe atherosclerosis of the aorta which involved approximately 75 per cent of the intimal surface. Distal to the coarctation, there was little atherosclerosis, with approximately 15 to 20 per cent of the intimal surface involved by yellow plaques. The internal mammary arteries were greatly dilated and hypertrophied measuring 1.6 cm. in circumference at their origins. The intercostal arteries were also dilated and hypertrophied and were anomalously situated just above instead of below each rib. The lungs were congested and edematous, and their arteries showed moderate atherosclerosis. Microscopically there were acute focal bronchopneumonia, emphysema, small organized infarction, and evidence of pulmonary vascular hypertension.



Fig. 5. The aneurysm on the right has been cut in cross section. Note the laminated layers of atheromatous material and the central thrombosed lumen of the false channel. The aortic channel is seen on the medial side of the aneurysm.

Ancillary findings included moderate cerebral atherosclerosis but no evidence of aneurysm formation. The kidneys and adrenal glands were not remarkable.

Discussion

The usual course of events with a dissecting aneurysm superimposed on coarctation of the aorta is rupture and death.[2] In reported cases of rupture distal to a coarctation, the aorta eroded into a bronchus, into the esophagus, into both bronchus and esophagus,[4] and into the left pleural cavity.[3] Rupture of the ascending aorta is much more common than rupture of the wall distal to the constriction. Rupture has been ascribed to hypertension and also to weak areas in the aortic wall.[1,3] The explanation for rupture or dissection distal to the site of coarctation, where blood pressure is lower, may also be found in a weakening of the wall.[1] Back pressure with or without contraction of the abdominal muscles can cause a marked rise in blood pressure. When this occurs against a rigid wall near the site of coarctation it can produce a tear in the wall.[4] Schuster and Gross[12] found that of all the aneurysms associated with coarctation, the most frequently seen are those of the intercostal arteries at their juncture with the aorta. These occur more frequently in the elderly and are apt to be very thin walled. Of a total of 57 aneurysms in 45 patients, 43 (75 per cent) arose from intercostal arteries at the aortic juncture, while only 9 (15 per cent) arose from the aorta above or below the coarctation. The dissecting aneurysm in our patient may have arisen from the rupture of one of these small intercostal artery aneurysms or from the rupture of an inherently weak area in the intercostal artery wall.

Summary

A long survival of coarctation of the aorta with dissecting aneurysm distal to the constriction is presented; the patient lived to age 65 years. This is also the longest documented survival of a patient with a healed dissecting aneurysm of the aorta; the diagnosis was made clinically 25 years prior to autopsy confirmation. Death was due to congestive heart failure, but cardiomegaly did not occur until sometime during the final 15 years of life.

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Cardiac involvement in pseudoxanthoma elasticum

Report of a case

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Pseudoxanthoma elasticum (PXE) is a heritable disease of connective tissues characterized by morphologic and functional alterations of the elastic fibers. It involves many parts of the body, notably the skin, mucous membrane, eye, heart, and blood vessels.[1] The association of the angioid streaks of the eye and the xanthomal ke lesions of the skin has been known as Gronblad-Strandberg syndrome.[2] Other clinical manifestations, such as hypertension, peripheral circulatory disturbance, and massive gastrointestinal hemorrhages may be prominent,[3,4] while the basic disease process remains unrecognized. The primary cardiac abnormalities in this condition are uncommon in the literature but may in some cases be the mode of presentation and indeed the cause of death. It is the purpose of this paper to report such a case.

Case study

A 36-year-old woman in her eighth month of pregnancy was admitted to Kingston General Hospital on July 2, 1964, because of congestive heart failure. The past history indicated that she had been a sick inf t, and had never had normal exercise tolerance. In 1952 she had cholecystectomy without complication and her 2 previous pregnancies, in 1949 and 1953, were uneventful. In 1960 she had an operation for uterine suspension, and at this time the chest x-ray film showed cardiac enlargement, and the electrocardiogram demonstrated numerous multifocal premature ventricular beats. Although she gave a vague history of dyspnea on exertion of approximately 3 years duration, it was not until September 1963, two months before she became pregnant, that there was definite limitation of activity because of shortness of breath. Her exercise tolerance became progressively worse and, by the twenty-second week of gestation, she had orthopnea and coughed up copious quantities of frothy blood-stained sputum. She was admitted to a military hospital overseas in May 1964 with acute pulmonary edema. The physical examination at that time revealed a gallop rhythm and an irregular heart rate due to multifocal ventricular beats. The patient was treated with rest, digitalis, diuretics, and chlorothiazide but she did not respond satisfactorily and was therefore transferred to Canada in July 1964.

When the patient was admitted to Kingston General Hospital, she was afebrile. The heart rate was 105 per minute and irregular and the blood pressure was 104/70 mm. Hg. The heart was enlarged, the apex beat was heaving in quality and palpable 13 cm. from the midsternal line in the fifth intercostal space. There were a Grade II apical midsystolic murmur and a protodiastolic gallop, jugular venous distension, and basal crepitation,

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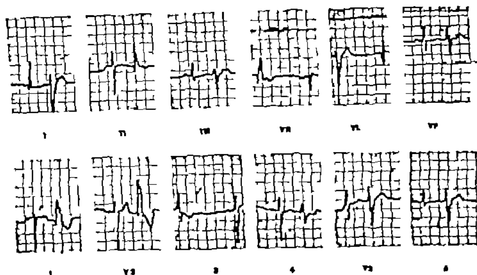


Fig. 1. The electrocardiogram shows sinus rhythm multifocal ventricular premature beats, and left ventricular hypertrophy.



Fig. 2. The chest x-ray film shows cardiac enlargement.

but there was neither peripheral edema nor hepatomegaly. The circulation time was 22 seconds. The ECG showed sinus rhythm with multifocal ventricular premature beats and left ventricular hypertrophy (Fig. 1). The chest x-ray film showed left ventricular hypertrophy (Fig. 2); in addition, on fluoroscopic examination revealed slight enlargement of the left atrium. On each side of the neck there was large yellowish retiform and papular lesion with intervening areas of atrophy. This had been present since childhood and the patient believed that the skin changes followed the topical use of kerosene for the treatment of repeated episodes of pharyngitis. She had no visual symptoms and the funduscopic examination was described as unremarkable. Laboratory investigations were all normal. She was not anemic, and repeated determinations of the serum electrolytes showed normal values. The Venereal Disease Research Laboratory and lupus erythematosus preparations gave negative results. She refused biopsy of the skin lesions on her neck. No definite etiologic diagnosis of the heart disease was made and she was classified as subject with primary myocardial disease.

In August, 1964, the patient gave birth to a normal male infant and she was discharged 6 days later on digitalis and sodium-restricted diet. Six weeks later she was seen in the cardiac clinic and was found to be free of heart failure, though cardiomegaly and ventricular premature beats persisted. The patient died suddenly at home on October 24, 1964.

Autopsy Findings

At autopsy there were large skin lesions characterized by light-brown discoloration which was associated with yellowish, reticular and papular lesions distributed symmetrically on both sides of the neck, axilla, and groin. The histologic sections showed deep dermal fibrosis and an accumulation of abnormal elastic fibers, which were granular, fragmented and curled (Fig. 3). These abnormal fibers gave positive staining characteristics for the elastica with Verhoeff aldehyde fuchsin, and orcein stains. This property was lost after elastase



Fig 3 The PXE lesion in the skin from the neck shows marked dermal fibrosis and heavy accumulation of dark granular elastic tissue in the dermis. (Hematoxylin, phloxin and saffron stain, X 116)



Fig 4 The right atrium shows a diffuse white endocardial thickening (arrow).



Fig 5 A whitish endocardial thickening is noted on the upper portion of the muscular septum of the left ventricle (arrow). A slight thickening of the chordae is noted in the anterior mitral leaflet

digestion. The elastic fiber had heavy deposition of calcium and were associated with a large amount of acid mucopolysaccharide in the connective tissue ground substance

The heart was enlarged and weighed 495 grams. All chambers were dilated, especially the left ventricle. The myocardium was of normal thickness but flabby The leaflets and orifices were normal, but the chordae tendineae of the anterior mitral leaflet were slightly thickened. The endocardium of both atria and the left ventricular outflow tract exhibited diffuse pearly white thickening (Figs. 4 and 5). In the posterolateral and posteroseptal wall of the left ventricle there was an area (5 by 4 cm.) of localized endomyocardial fibrosis which resembled a healed infarct but no occlusive coronary lesion was found to account for this. Microscopically the endocardium showed nodular and plaquelike thickening due to an increase of collagen and elastic fibers (Fig 6). The elastic fibers showed changes identical to those described in the skin lesion. The left bundle branch and the second portion of the

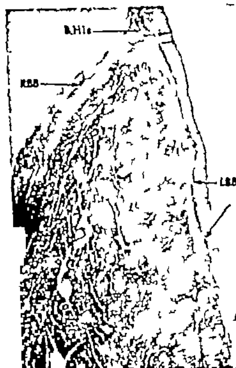


Fig. 6. The microscopic section of the ventricular septum shows the bundle of His and its branches. The left bundle branch (*LBB*) is encased in the thickened and fibrosed endocardium, in which abnormal elastic fibers are seen overlying the *LBB*. The right bundle branch (*RBB*) is unremarkable but the endocardium also shows fibrosis. (Hematoxylin phloxin, and saffron stain, × 48.)



Fig. 7. The section of the left-ventricular septal endocardium shows abnormal elastic tissues (arrow) and thick collagen fibers. The myofibers of the *LBB* appear to be slightly atrophic. (Hematoxylin phloxin and saffron stain, × 738.)

right bundle branch of the conduction system were encased in the thickened endocardium which contained fibrous and altered elastic tissue (Fig. 7). The S-A and A-V nodes were not remarkable and showed no increase in elastic tissue. The lesion of endomyocardial fibrosis in the posterior and lateral wall of the left ventricle contained only fibrous tissue.

Grossly the coronary arteries and the peripheral arteries were unremarkable, but, microscopically there was calcification and fragmentation of the elastica interna of the muscular arteries. Similar elastic alterations were found in the adventitia of the main pulmonary artery and, rarely, in the aortic media. The posterior segments of the eye were removed for examination but showed no angioid streaks grossly. This was perhaps due to the detachment of the retina when the eyes were removed. Microscopically the Bruch membrane was basophilic and appeared to be rigid with fragmentation. In keeping with the postpartum state, the uterus was about twice the normal size. No significant change was seen in the vessels of the uterus or of other organs. The cause of death was thought to be cardiac arrhythmia.

Discussion

This is a typical example of PXE with cutaneous, ocular and cardiovascular involvement. The cardiac lesion was advanced and probably accounted for the congestive heart failure during pregnancy and the persistent arrhythmia that dominated the clinical picture. In a survey of 200 cases of PXE reported in the literature, Eddy and Farber[4] noted that, among the associated clinical manifestations, visual difficulty occurred in 29 per cent, angina pectoris in 19 per cent, radiologically demonstrable calcification of peripheral arteries in 14 per cent, intermittent claudication in 18 per cent, severe psychic disturbance in 6.5 per cent, epilepsy in 29 per cent, and massive gastrointestinal hemorrhages in 13 per cent. The diverse clinical manifestations probably result from the anatomic and functional derangement of the elastic fibers in the various tissues and organs involved.

Cardiac involvement in PXE may occur but its possible role in the development of heart failure has not been stressed in the past. Eight cases have been reported in the literature with proved endocardial and/or valvular involvement (Table I). The first case of PXE with endocardial involvement was recorded by Balzer in 1884.[7] The lesion was described as a whitish-yellow endocardial thickening in the right atrium and in the ventricular trabeculae. The cardiac lesion was apparently not related to the cause of death. The case described by Von Tannenhain[8] was diagnosed grossly as chronic mitral endocarditis but no histologic study was made to confirm the lesion. McKusick[11] and Carlborg and associates[4] each described a patient who had lesions in the atrial endocardium and to a mild degree in the valves. Both patients died of causes unrelated to the heart. The cases reported by Prick, Coffman and Sommers,[13] and Wilkins and Sommers[5] were probably the only 3 patients that died in congestive heart failure due to a valvular deformity from this disease. Yoffee and Derbes[1] reported the case of a 19-year-old girl with mitral stenosis and congestive failure presumably due to PXE, but no pathologic studies were made to confirm the clinical diagnosis. The clinical manifestations in cases with cardiac PXE are variable and nonspecific. These include cardiac enlargement, cardiac murmurs, arrhythmias, atrial fibrillation, nonspecific ECG changes, and

Table I. Reported cases with cardiac involvement in PXE

Authors	Year	Patient		Pathologic lesion in heart	Probable cause of death
		Age	Sex		
Balzer	1884	49	M	Whitish-yellow endocardial thickening in right atrium and left ventricular trabeculae	Pulmonary tuberculosis
Von Tannenhain	1909	49	F	"Chronic mitral endocarditis" (no histologic study)	Generalized arteriosclerosis, nephritis, and gastrointestinal hemorrhage
Prick	1938	48	F	Thickened whitish-yellow patches on mitral valve	Congestive heart failure and cerebral complication
Reiner[15]	1955	37	F	Thickened and opaque endocardium of atria and left ventricle	Not clear
McKusick	1956	63	M	Endocardial thickening of right atrium and trabeculae and posterior leaflet of tricuspid valve	Accidental mercuric poisoning
Coffman and Sommers	1959	68	F	Whitish-yellow plaques, left atrial endocardium thickening and calcification of mitral valve and mitral stenosis	Congestive heart failure
Wilkins and Sommers[13]	1959	63	F	Thickening of mitral valve and mitral stenosis	Congestive heart failure
Carlborg and associates	1959	61	F	Diffuse grayish-yellow thickening of left atrium and plaques on valves	GI [illegible]

hypertension. Our patient showed cardiomegaly, arrhythmia, and congestive failure associated with pregnancy and then she died suddenly, presumably of an arrhythmia. Because of the nonspecific clinical manifestations, the basic cardiac lesion could not be suspected during the life of the patients.

It is interesting to note that in this case both the ventricular arrhythmia and the cardiac decompensation were increasingly more difficult to control in the latter part of the pregnancy, and so the clinical diagnosis of idiopathic heart disease associated with pregnancy was considered. As shown in the study of Johnson and associates,[1a] this diagnosis was rendered less likely due to the lack of histologic evidence of widespread myocardial degeneration, necrosis, and fibrosis. It is not unreasonable to speculate that cardiac decompensation in this case was accentuated by the effect of pregnancy on the already-diseased elastic tissue. McCaughey and associates noted that gastrointestinal bleeding in patients with PXE was encountered more frequently during pregnancy. These authors stated that the elastic tissue underwent degeneration during pregnancy, and a biopsy of the abdominal striae during gestation showed an obvious disintegration of the elastic fibers. It is possible that pregnancy might aggravate the disease process (in PXE) of the elastic tissue in the endocardium.

The advanced lesion of PXE in the present case was found to involve the atrial and ventricular endocardium, which is similar to the observations that are noted in endocardial fibroelastosis. The involvement of the bundle branches by the lesion might be responsible for the development of multiple ventricular premature beats and arrhythmia. It has been observed that the mural endocardium is a complex structure which consists of 6 separated layers. Little is known about either the function of the endocardium as a whole or the functions of the individual layers. Davies[1] suggested that during life the endocardium must be continuously varying its structures under constantly changing pressures. According to him, the elastic tissue and perhaps the smooth-muscle layer play a part in the recoil mechanism. It seems probable that the adjustments made to stretch and recoil would vary in different areas of the endocardium, since it is not a uniform structure. It is thicker in the atria than in the ventricles; it is thinner in the ventricular inflow tracts than in the outflow tracts. These are probably related to functional differences. Therefore, it is not inconceivable that a variety of disease processes that alters this delicate but complex structure would also lead to a variable disturbance of its function.

Since PXE is a systemic dysplastic disorder of elastic tissue,[1] the rarity of cardiac involvement, as reflected in the literature, is difficult to explain. Carlborg[1] expressed an opinion that this may be related to the small amount of elastic tissue which is normally present in the heart. However, it is apparent that the amount of elastica is not a factor in determining the organ involvement, because the PXE lesion is also uncommon in the aorta, which, nevertheless, contains abundant elastica.

Although the symptoms and signs of heart disease in PXE are common, the nonspecificity of the manifestations renders the cardiac assessment difficult. Without a pathologic examination of the heart, the extent of PXE involvement is unpredictable from the clinical point of view. It cannot be overemphasized, however, that in a young person with Grönblad-Strandberg syndrome, cardiac manifestation may, on some occasions, constitute an important part of the symptom complex.

Summary

A 36-year-old woman with typical skin manifestation of pseudoxanthoma elasticum presented with arrhythmia, cardiomegaly, and congestive failure during pregnancy and died suddenly, presumably of cardiac arrhythmia. Autopsy revealed systemic involvement with PXE lesion in the skin, the eye, and the cardiovascular system. The cardiac involvement is considered to have been responsible for the clinical manifestations. The possible role of PXE in the heart in the genesis of the cardiac failure and arrhythmia are discussed.

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Review

Endomyocardial fibrosis in Uganda (Davies disease) Part I*

An epidemiologic, clinical, and pathologic study

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Small endocardial scars are common findings at autopsy in all parts of the world. They may form in almost any cardiac disorder; most of these scars represent organized thrombi, healed foci of endocarditis, or healed myocardial infarcts. As a rule they do not interfere with cardiac function. In 1948, however, Professor J. N. P. Davies described a disease characterized by broad, thick scars on the mural endocardium. The disease was acquired, progressive, and fatal; it struck children and young adults and, in the autopsy population at Mulago Hospital in Uganda, it accounted for no less than 15 per cent of all deaths from congestive failure. Since those early days endomyocardial fibrosis (EMF) has come to be recognized in Uganda as a distinct clinicopathologic entity.† The cause remains unknown and the pathogenesis is obscure because only the end stage of the disease has been recognized at autopsy. In an attempt to delineate the pathogenesis, we studied all cases of obscure heart failure presented at autopsy at Mulago Hospital during an 18-month period.

Historical aspects

Since the turn of the century a number of European and American investigators have reported examples of obscure heart failure associated with endocardial scarring.‡ There are 55 cases reported in these 15 papers. In each, the patient died of heart failure and, at autopsy, the majority had endocardial scars or endocardial thrombi. Some had minimal focal fibrosis of the endocardium; in others, the fibrosis was extensive. The descriptions of only 4 of

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*Part II of this study will appear in the [illegible] issue of the Journal.

†Professor Davies first used "endomyocardial fibrosis" as a descriptive term and subsequent investigations have confirmed his belief that EMF is a unique entity. In the recent literature, however, the term endomyocardial fibrosis has been applied to hearts with lesions unlike those Davies described. To exclude these, we have used "Davies disease" in the title.

‡References are given with Part II.

these 55 hearts* resemble endomyocardial fibrosis and as a group these rare descriptions from America and Europe have no distinguishing features or recurring pattern of endocardial scars. In Uganda however large endocardial scars characterize a common intrinsic heart disease in which the endocardial scars involve specific sites and occur in predictable combinations.

During the early 1940s Dr A. W. Williams and Dr R. S. F. Hennessey became aware of an unusual form of heart disease in Uganda [7] but Bedford and Konstam gave the first report of this disease at a meeting of the British Cardiac Society in 1946. During World War II they studied 40 West African soldiers in the Middle East. Seventeen of them were studied post mortem and although the authors gave few pathologic details, they did mention a variety of abnormalities, which included in some hearts an obvious "extensive subendocardial fibrosis [and] necrosis without appreciable inflammation." At about the same time Edge[19] reported a remarkable case from West Africa. After a 41 year-old soldier had contracted syphilis he was treated with neoarsphenamine and died 7 months later of intractable heart failure. There was thickened endocardium in both ventricles and a greenish red thrombus filled the left apex. These 2 reports solved no problems, but seen in retrospect they heralded the current interest in the African cardiopathies.† In 1947 Davies encountered in quick succession at autopsy 3 hearts that aroused his interest each had dense scarring of the mural endocardium. In his first report[19] he described fibrosis of the ventricular apices that "crept" up over the columnae carneae. As his review of autopsy records at Mulago Hospital revealed it was a common condition second only to syphilitic aortitis as a cause of fatal intrinsic heart disease. In subsequent studies Davies and coworkers[20,27] further clarified the entity. In summary (1) They adopted the descriptive term "endomyocardial fibrosis." (2) They defined specific sites of mural endocardial involvement that occurred alone or in combination and with experience could be diagnosed ante mortem. (3) Clinically there was mitral and/or tricuspid incompetence that correlated with the left and right-sided lesions found at autopsy. (4) They recognized a preponderance of patients from the immigrant "Rwanda Burundi" ethnic group. (5) Though the pathogenesis was not clear subendocardial muscle damage seemed to precede endocardial thrombosis and this was followed by organization and fibrosis. (6) There was myocardial damage which was most marked beneath the endocardial scars.

Somers and Williams[23,24] described electrocardiographic abnormalities and the phonocardiographic findings of atrioventricular incompetence in EMF. Hemodynamic studies by Shillingford and Somers[3] showed that patients with left-sided lesions had mitral insufficiency and pulmonary hypertension and patients with right-sided lesions had high systemic venous pressure tricuspid incompetence and ascites.

During this period of excitement in Uganda Gillanders[26] and Becker and associates[27] described 2 cardiopathies in South Africa that were characterized by dilated failing hearts with patchy endocardial scarring. Gray[28] described 2 Europeans who had lived in Nigeria and died of failing hearts with endocardial scars and thrombi. These reports provoked the conjecture that all these African cardiopathies might be the same disease. Abrahams[29] then described a syndrome in Nigerians characterized by acute carditis and fibrosis of the left ventricle. Clinically the carditis resembled rheumatic carditis and the ventricular fibrosis shortened the chordae tendineae of the mitral valve. In addition there was the signal finding of "paravascular collections of cells indistinguishable from Aschoff nodes." Was this disease as he suggested "an unusual expression of the rheumatic process" and were the cardiopathies of East and South Africa an atypical rheumatic heart disease as well? Later in clinical studies Abrahams[30] described findings that were similar to those reported from Uganda for both left- and right-sided lesions. Abrahams and Brocklen

*(1) The case report of Mickanick, (2) the fifth case of Black and Fowler,[13] (3) the second case of Farquer and (4) the fourth case of Lynch and Watt.

†Cardiopathy is used throughout ... heart disease of unknown cause. We prefer cardiopathy to cardiomyopathy here because the latter implies primary disease of the myocardium, an unwarranted presumption at present.

found high antistreptolysin-O titers in half the patients with left ventricle lesions and Aschoff bodies in 8 hearts of the 13 that were autopsied.

Further descriptions of the South African cardiopathies by Higginson and associates,[37,38] Chatgidakis and Barlow[39] and later Becker[40] have allowed accurate comparisons. Most investigators now believe that the 2 South African cardiopathies are the same disease but that endomyocardial fibrosis of tropical Africa is different from these South African cardiopathies.[41-44] However agreement on the latter point is not universal.[45]

In a more recent pathologic study of cardiopathies in Nigeria, Edington and Jackson[46] found no evidence of rheumatic carditis and they proposed a broader concept of EMF. They described 29 hearts that portrayed a spectrum which varied from dilatation and hypertrophy without appreciable endocardial scarring (which they called "heart muscle disease") at one end through an intermediate group to frank endomyocardial fibrosis at the other end. For clinical and epidemiologic reasons, Parry and Abrahams[47] maintained that endomyocardial fibrosis was distinct from heart muscle disease. They described the natural history of EMF as a febrile pancarditis which began in the rainy season and in some patients, ended fatally in about 2 weeks. Other patients, who survived the acute attack died later in the "subacute" stage while in still others the process "burnt out" and enabled long survival.

Heart diseases that resemble those of Davies disease have come from other countries in tropical Africa* and from countries beyond Africa.† One heart which was reported from Australia[62] lacked the distinguishing features, but in South Africa Brink and Weber[64] have described typical lesions in the heart of a Caucasian man who had lived in the Congo (Kinshasha). Time will probably tell whether all of these *conditions are manifestations of the same* disease. Meanwhile a WHO group is attempting to bring together and evaluate modern views on the cardiopathies.[65]

Methods

During the study period (April 1962 through October 1963) 2,427 patients died in Mulago Hospital and 685‡ of these were autopsied. Of the 685, 467 were male and 218 female subjects, a ratio of about 2:1. Sixty-five patients (9.5 per cent) died of

*The Sudan, Ghana, Kenya, and Tanzania, the Congo (Brazzaville), Gabon, the Congo (Kinshasha)

†Malaya, Ceylon, South India, Brazil, Colombia, and Japan

‡There were 249 forensic autopsies during this period, but most of these came from outside the hospital and are not counted in the group

*Table I. Diagnoses for the 65 autopsied subjects with fatal heart disease**

Diagnosis	Ethnic group			
	Ganda	*Rwanda*	*Other*	*Total*
Rheumatic heart disease (active and inactive, with and without SBE)	10	4	9	23
Endomyocardial fibrosis	0	13	3	16
Congenital heart disease (including one subject with neonatal fibroelastosis and two with Lutembacher syndrome)	6	1	4	11
Hypertension (including those with renal disease)	2	2	4	8
Luetic aortitis	1	0	1	2
Coronary atherosclerosis	1	0	0	1
Acute bacterial endocarditis (no underlying disease evident)	1	0	0	1
Ruptured aortic aneurysm with cardiac tamponade	1	0	0	1
Dilatation and hypertrophy, no other features	0	0	2	2
				65

*Excluded are cases of fatal anemias and infections in which heart failure was only a terminal event.

Table II. Clinical, epidemiologic, and microscopic data on 16 patients who died of EMF

Case No.	Age	Ethnic group	Sex	Resident subcounty	Body wt. (Kg.)	Heart wt. (Gm.)	Pericardial fluid (ml.)	Right border notch	Fibrosis of right ventricle
1	27	Rwanda	M	66 k	63 7	350	100	0	A
2	26	Ahulu	F	76 e	47 2	410	?	+	C
3	28	Rwanda	F	66	41 8	276	0	0	0
4	25	Rwanda	F	75 b	68 3	420	20	0	A
5	22	Rwanda	F	65 b	57 8	240	Much	+	B
6	10	Rwanda	M	74	30	300	50	+	B
7	40	Rwanda	M	73 b	56 9	375	300	0	A
8	26	Rwanda	F	73 g	54 5	382	275	+	B
9	12	Rwanda	F	66 e	36 1	180	1500	+	B
10	6	Rwanda	M	66 h	?	230	6	0	A
11	35	Rwanda	F	66 k	35 8	420	200	+	B
12	19	Ankole	M	66 e	60 5	300	800	+	B
13	6	Kiga	M	73 d	17 5	240	Little	0	0
14	40	Rwanda	F	68	32 8	305	0	+	B
15	4	Rwanda	M	66	13 2	70	25	+	B
16	10	Rwanda	F	73	21 6	178	200	0	A

*Atlas of Uganda, ed. 1, Department of Lands and Surveys, Kampala, Uganda, 1962, pp. 34, 35.
†A, Not involving papillary muscles; B, extending over papillary muscles; C, Encasing papillary muscles.
‡A, Without valvular impairment; B, with valvular impairment.
§Scar plus mucin matrix plus fibrin.
‖Both active and healed lesions.
¶Newly formed collagen bundles are separated by mucin, but they were not necrotic.
**Microscopic foci, not evident grossly.

intrinsic heart disease (Table I). Of the 65, 16 patients died of EMF, and these 16 are the basis of this study (Table II). The clinical record of each was studied and correlated with the autopsy findings. One autopsy (No. 13) was limited to the thorax, but the others were unrestricted. The hearts were opened as soon as possible and the involved surfaces were photographed. The whole hearts were then fixed for 4 days in refrigerated buffered formalin. This produced uniform fixation without recognizable autolysis or acid hematin deposits. Two of the hearts were inflated with a formol-gel solution before dissection to preserve the contour. Blocks were cut from 12 standard sites and from all gross lesions. All chambers, all valves, and attached major vessels were studied microscopically. The blocks were cut so that the contour of the heart was preserved and the hearts would be available for further study. Slides from all of these blocks were stained with hematoxylin and eosin and by Movat's pentachrome method. Other stains—aniline blue, PAS, Giemsa, PTAH, Gomori methenamine-silver, acid mucopolysaccharide (AMP), acid fast, and oil red O (frozen section), and preparations for iron and elastica—were used on selected blocks. Sections of all organs were stained with hematoxylin and eosin and with Movat's stain. For comparison, 28 hearts without EMF were also studied, which made a total of 44 hearts that were studied by this special routine (Table III).

The selection of hearts for inclusion in the series posed a number of problems. One heart had a milky but not a measurably thickened endocardium. This heart was excluded when microscopic study revealed rheumatic pancarditis. Another heart had small patchy endocardial scars unlike those typical of EMF and microscopically showed no specific or characteristic changes, so this heart was also excluded. Another problem heart had rheumatic mitral stenosis with superimposed bacterial endocarditis and a thick, broad endocardial scar at the apex of the right ventricle. At

Fibrosis of posterior wall, left ventricle‡	*Fibrosis of apex left ventricle*	*Maximum thickness of endocardial scar (mm.)§*	*Interstitial AMP*	*Myocardial degeneration*	*Collagen necrosis*	*Endocardial calcification*	*Vascular changes¶*
B	0	10 0 LV	+	+	0	0	+
0	+	13 0 RV	+	+	+	0	+
B	0	7 0 LV	+	+	+	0	+
B	+	15 0 LV	+	+	+	0	+
0	+	4 0 LV	+	+	+	0	+
B	+	1 0 LV	+	0	+	0	+
B	+	2 0 LV	+	0	+	0	+
B	+	3 0 LV	+	0	+	+	+
0	+	4 0 RV	+	0	+	+**	+
B	+	1 0 LV	+	0	+	+	+
0	+	3 0 RV	+	+	+	0	+
A	+	3 0 RV	+	0	+	+	+
A	0	0 1 LV	+	0	+	0	+
B	0	4 0 RV	+	0	+	0	+
A	0	5 0 RV	+	0	+	+	0
B	+	2 0 LV	+	+	+	0	0

Table III. Diagnoses in 44 subjects in which the hearts were studied and compared

Diagnosis	*No. of hearts*
Endomyocardial fibrosis	16
Rheumatic heart disease	11
Syphilitic heart disease	2
Lutembacher syndrome	2
Dilated and hypertrophied hearts without other lesions (idiopathic hypertrophy)	2
Kwashiorkor	5
Burkitt tumor	1
Typhoid fever	1
Trypanosomiasis	1
Malaria	1
Miliary tuberculosis	1
Measles	1
Total	44

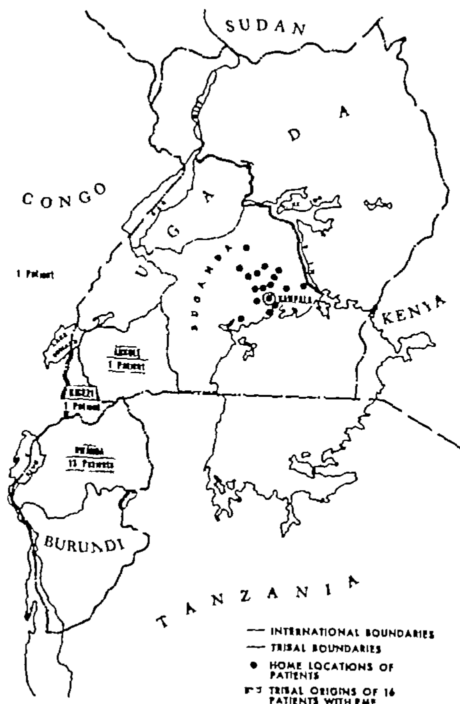
The 16 hearts with EMF were studied in conjunction with 17 hearts with other intrinsic focal lesions (rheumatic, luetic, Lutembacher's, and idiopathic hypertrophy) and with 11 hearts from subjects without heart disease.

first we thought this was an example of combined rheumatic heart disease and endomyocardial fibrosis, but the mural scar did not contract the right ventricle and there were no microscopic or other gross features of EMF so this heart was excluded from the series. The last problem heart had a slightly thickened endocardium that was cloudy in some areas but white and opaque in others. Microscopically this heart had endocardial damage behind the posterior mitral leaflet a typical location for endocardial damage in EMF and it had other microscopic characteristics of EMF so it was included in the study

In 1964 one of us (D H C) visited departments of pathology in Dakar Accra Ibadan Brazzaville Onderstepoort Johannesburg Capetown and Lourenço Marques to study and compare the African cardiopathies.

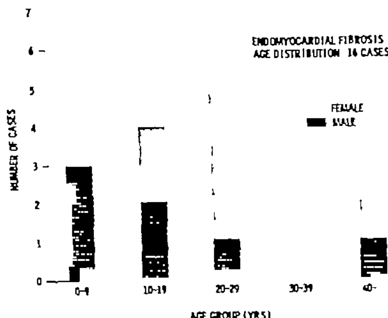
Results

Epidemiologic findings Table II lists some of the epidemiologic clinical and



pathologic data for the 16 patients. Each had migrated to Buganda* in early childhood. Thirteen of the 16 (81 per cent) were from the ethnic group Rwanda; in an autopsy population comprised of only 24 per cent Rwanda. Two were from southwest Uganda and one was from the Congo (see map). The Rwanda in Uganda are a well recognized group. They originate in the small highland countries of Rwanda and Burundi and they come to Uganda in search of a better livelihood. Their incomes are low (many are in the employ of the Ganda) and the majority do menial agricultural work. Unfortunately, almost nothing is known of the types of fatal heart disease in their home countries of Rwanda and

*Buganda is the home territory of the Ganda tribe



Graph I. Age distribution of cases of endomyocardial fibrosis.

Burundi. As striking and perplexing is the fact that the Ganda, the largest ethnic group in Uganda and accounting for 36 per cent of the autopsies, contributed no patients with EMF. The selection of patient cannot explain this bias because cardiac patients were admitted and studied regardless of tribal origin. For instance, the Ganda contributed slightly more cases of rheumatic heart disease (44 per cent) than expected; the Rwanda contributed less (17 per cent) than expected (Table I). In a recent clinical study at Mulago Hospital,[44] 60.5 per cent of those with EMF were Rwanda. Each of the 16 patients with EMF lived in Buganda when symptoms began but the ancestral territories of 15 of them were far to the southwest (see map) and the sixteenth patient (No. 2) came from the Congo (Kinshasha).

The youngest patient was 4 years old, the oldest was 40, and the average age was 21 years. More died in the third decade than in any other decade. Graph I shows the 9 female and 7 male subjects by age group. There is a striking preponderance of female subjects in an autopsy population that favors men by more than 2 to 1. This female predominance is more striking in the older age groups. There was no obvious seasonal pattern. The 16 deaths were distributed throughout the year and the 4 patients with short clinical histories died in January, March, July, and October respectively. All were in the low income group and ate a predominantly farinaceous diet that included cassava, sweet potato, wild spinach, ground nuts (peanuts), and occasionally plantain ("cooking bananas" —*Musa* sp.). Their intake of animal protein (milk or meat) was rare and minimal. None drank alcohol excessively, although one admitted drinking waragi, an illegal but popular ethanol distillate.

Lesions comparable to those of Ugandan EMF were not found in the patients of Johannesburg, the Capetown area, Lourenço Marques, or Dakar. The hearts of some patients in South Africa contained multiple discrete mural thrombi. These thrombi were dark red, small (up to 1.0 cm. in diameter), and fixed to the endocardium of the intratrabecular recesses of the apical and outflow areas of the ventricles. In hearts with long-standing disease these thrombi had organized to patchy and sometimes diffuse mural scars. These South African hearts were very different, grossly and microscopically, from the Ugandan hearts with EMF. In Accra and Ibadan there were hearts with gross endocardial lesions that were somewhat

milar to those of the Ugandan EMF hearts but as a group the hearts in Accra and Ibadan lacked the striking localization of gross lesions which were seen in the Ugandan hearts. Comparable microscopic sections were not available for study so no definite conclusion could be reached about whether or not the East and West African cardiopathies are identical. No hearts were available for study in Brazzaville.

Clinical findings

GENERAL. The main symptoms in patients with left sided lesions were cough, progressive dyspnea of effort, and sometimes hemoptysis. In patients with predominantly right sided lesions the main symptoms were abdominal swelling from ascites, hepatomegaly, and peripheral edema. Sometimes the history suggested initial symptoms of left sided heart failure followed by those of congestive heart failure. The onset was usually insidious, it mounted in severity over a period of several weeks, and ended fatally in several months to several years. The most rapid clinical course was 12 days (No. 1). This patient had had an episode of chest pain, fever, and hemoptysis 2 months before death. Nearly all of the patients who were questioned admitted past episodes of fever, and in 5 patients (Nos. 1, 3, 4, 7, and 10) there was fever just before or during the onset of cardiac symptoms. In 3 other subjects (Nos. 13, 15, and 16) unexplained fever of 100° to 103° F persisted for several weeks during the terminal hospitalization. One patient (No. 8) claimed his illness began with pain in the legs and joints, but none of the others had pain in the joints or other evidence of rheumatic fever. Three patients had atrial fibrillation and of these two (Nos. 7, 8) had predominantly left ventricular lesions and one (No. 14) had a lone right ventricular lesion. One patient (No. 2) had aborted 2 weeks before the sudden onset of her fatal illness and 2 patients (Nos. 3, 8) were lactating at the time of death. Three patients (Nos. 13, 14, and 15) had unexplained jaundice during the terminal illness. In one (No. 15) this was probably a hemolytic episode because the jaundice was transient and was followed by a reticulocytosis. Four patients (Nos. 7, 9, 12, and 15) had pericarditis with effusion. In one patient (No. 9) this was chronic for 5 months and recurred 4 years later during the terminal illness. Diet, illnesses, and possible exposures to toxins and poisons were impossible to evaluate. One patient (No. 14) was cachectic and another (No. 15) a boy 4 years of age was suspected of having mild kwashiorkor. At autopsy a fatty liver was revealed but none of the other stigmas of kwashiorkor. The remaining 14 were not undernourished.

LEFT VENTRICULAR EMF. Patients with predominantly left ventricular EMF often had classical signs of mitral insufficiency which was characterized by a high pitched, frequently squeaking pansystolic murmur which radiated to the axilla. In addition features of pulmonary hypertension were usual—a left parasternal lift of right ventricular hypertrophy, a palpable lift in the pulmonary area, and a loud pulmonary closure sound. Signs of pulmonary congestion were evident and signs of secondary congestive heart failure were frequently present. The electrocardiograms showed low voltage QRS complexes, T wave changes, and a mitral configuration of the P wave. Right axis deviation and clockwise rotation were common. Occasionally the R wave in V_1 seemed abnormally prominent. There were 2 patients with atrial fibrillation (Nos. 7 and 8) and both had predominantly left ventricular lesions. The x-ray films showed a normal or enlarged heart shadow and congested lung fields sometimes with pleural effusion and marked prominence of the pulmonary veins. These patients were in respiratory distress from pulmonary edema and hypoxia.

RIGHT VENTRICULAR EMF. In patients with predominantly right ventricular EMF there was the murmur of tricuspid insufficiency. The systemic venous pressure was grossly raised often to the angle of the jaw with active systolic pulsation, the liver was large and pulsating, ascites, peripheral edema, and splenomegaly were present. The ECG showed P mitrale in some patients but no right ventricular preponderance. The QRS voltage was low and the T waves were abnormally flat or inverted. One patient (No. 14) had atrial fibrillation. The x-ray films revealed a greatly enlarged cardiothoracic ratio which was caused by marked enlargement

of the right atrium. This formed the right border in the straight PA projection. Calcification of the fibrosed right ventricular apex was seen on straight projection (No. 12)

COMBINED LEFT AND RIGHT LESIONS With left and right-sided heart disease the left sided features usually dominated but it was sometimes impossible to be certain which ventricle was more severely diseased

Laboratory findings A variety of laboratory tests were performed in each patient Serum gamma globulins tended to be high The gamma globulins were 40 27 35 54 28 48 and 37 per cent of total proteins in patients Nos. 1 3 8 11 13 14 and 16 respectively Six patients (Nos. 1 3 7 8 13 and 14) had an eosinophilia that ranged up to 64 per cent. Three of these patients had intestinal parasitism (hookworms, ascarids, or tapeworms) and one had bancroftian filariasis (No. 7) The aspirated pericardial fluid which was amber and protein rich (up to 6 gm per 100 cubic centimeters) clotted on removal and contained many lymphocytes.

Gross cardiac findings The more striking gross features are summarized in Diagram A.

PERICARDIUM In one heart (No. 9) there was a broad fibrous adhesion between the parietal and visceral layers at the apex of the right ventricle and there were nodular collections of lipofuscin on the serosal surface (Fig 9 top left) This patient had had repeated pericardiocenteses.

PERICARDIAL FLUID There was excessive pericardial fluid in 10 hearts and in 3 of these (Nos. 9 12 and 15) pericardial fluid had been aspirated during life to relieve cardiac tamponade. The largest amounts of fluid were in those with severe scarring of the right ventricle.

EXTERNAL LESIONS There was right atrial dilatation in each heart and in those with severe right ventricular fibrosis, the right atrium was greatly enlarged sometimes dwarfing the other chambers (Fig 11 bottom left and top right Fig 12 top left) In 9 hearts there was an indrawing or contraction of the right border of the heart just above the right ventricular apex (Fig 4 top left Fig 5 middle left Fig 8 top left Fig 9 top left Fig 10 bottom left and Fig 11 top left) This right border notch was accentuated by dilatation of the right ventricular outflow There were occasional flat white epicardial patches ("soldier's patches) Five hearts had a distinctly slimy or slippery epicardium and one of these had fine nodules or beading of the epicardial vessels. Most of the hearts had congested epicardial capillaries, but the

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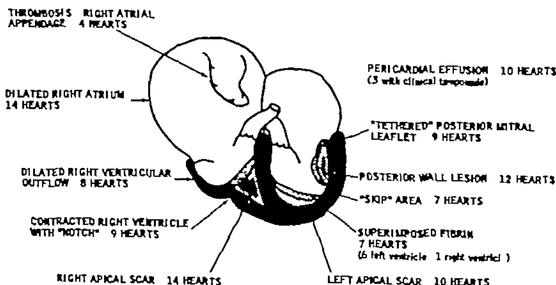


Diagram 1 Diagrammatic summary of the gross features of 16 cases of endomyocardial fibrosis.

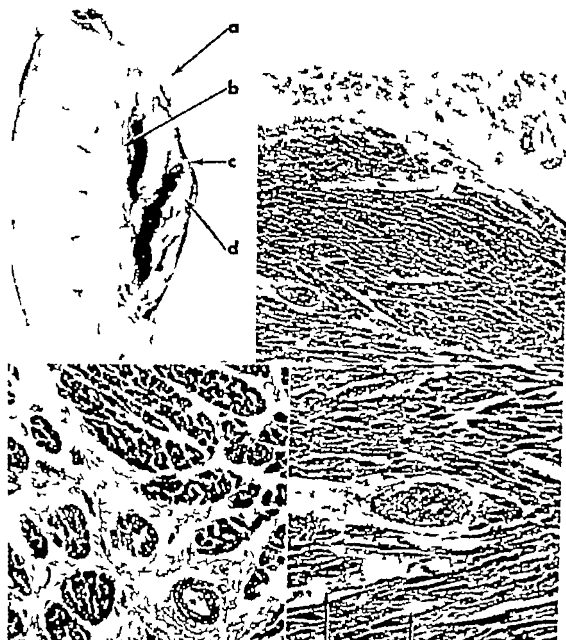


Fig. 1. Top left. This photograph was taken through the left ventricle to show the bulk lesion situated behind the posterior mitral leaflet. The lesion extends down the posterior wall, surrounds the posterior papillary muscle and tires all but the free margin of the leaflet (See also Color Plate 1, top left.) The surface area ( ) is mixture of fibrin and red cells, and the main lesion (d) is fibrin. The dark areas are open channels of red cells, and the gray are (b) ... zing AMP. (Heart No. 1, posterior wall of left ventricle × 2. AFIP Neg. 66-7381.)

Top right. This ... through the posterior wall behind the posterior mitral leaflet. The surface layer is organizing matrix of mus... containing many Anitschkow myocytes and scattered lymphocytes, plasma cells, and stellate and rounded mesenchymal cells, some of which contain intracytoplasmic AMP. Collagen fibers are beginning to form ... of the vessels in the underlying myocardium are thick walled and have narrowed lumens. The arteriole at the lower left ... enlarged below. (Heart No. 1, posterior wall of left ventricle. Movat × 42. AFIP Neg. 66-1429.)

Bottom left. This shows a small portion of the wall of the left ventricle behind the attachment of the posterior mitral leaflet. The muscle bundles are separated by AMP and collagen is beginning to form between the bundles. (Heart No. 1, left ventricle. Movat × 90. AFIP Neg. 66-1641.)

Bottom right. This is ... enlargement of the intramuscular arteriole seen above. The wall is thickened and the lumen narrowed. There is proliferation of the intima and swelling of the muscularis by AMP. Some collagen has replaced muscularis. Numerous lymphocytes and Anitschkow myocytes have infiltrated the wall, and there is surrounding scar tissue. Strands of interstitial ... tissue lie ... the arrow tips. (Heart No. 1, posterior wall of left ventricle. Movat × 100. AFIP Neg. 66-1430.)



Fig. 2. Top left. This is the aortic valve view of the left ventricle (see Color Plate I, bottom left). Note the solid fibrin thrombus in the apex. This is separated from the lesion of the posterior wall by a zone of uninvolved endocardium at the base of the posterior papillary muscle. The lesion of the posterior wall encroaches on the outflow area. Note the otherwise uninvolved outflow area, the normal chordae tendineae, and the normal aortic cusps. The apical lesion does not contract the apex. (Heart No. 4, left ventricle, aortic view. × 0.6. AFIP Neg. 66-7392.)

Top right. This horseshoe-shaped subendocardial focus of myocardial degeneration partially surrounds a thick-walled arteriole with a compromised lumen (arrow). (Heart No. 2, anterior wall, left ventricle. Movat. × 35. AFIP Neg. 66-4065.)

Bottom left. This is a similar area of myocardial degeneration, immediately beneath the epicardium. (Heart No. 3, posterior wall, left ventricle. Movat. × 80. AFIP Neg. 66-1452.)

Fig. 3 Top left. This is a section through the posterior wall of the right ventricle. The posterior tricuspid leaflet is at ( ). A fibrin thrombus ( ) covers the inflow of the right ventricle engulfing the posterior nd medial papillary muscles and their attached chordae tendineae. The translucent gray layer at (*b*) is organizing matrix of mucin. The apex of the right ventricle is obliterated and contracted by scar tissue. The fibrin thrombus stops bruptly at the beginning of the outflow. There was a smaller but similar plaque of fibri t the pex of the left ventricle, and the endocardium of the posterior wall of the left ventricle was minimally scarred. (Heart No. 2 posterior wall of right entricle × 2 AFIP Neg 66-7385.)

Top right. This is through the posterior right ventricular wall at (*b*) in the preceding picture. The top layer ( ) is fibrin. Although it contains scattered blood cells and t its depth few mesenchymal cells containing AMP t is essentially pure fibrin and covers sharply defined zone of organizing acid mucopolysaccharide (*b* and). This organizing layer is less ascular in its pper portion (*b*) and more ascular in its lower portion ( ). The original endocardium is represented by a few collagen and elastic fibers which at (*d*) are fragmented and partly obscured by agonal hemorrhage. (Heart No. 2 posterior wall of right ventricle Movat, × 21 AFIP Neg 66-2356.)

Middle right. This is section through the circumflex branch of the left coronary artery. The intima is thickened by plaqu of fibrin and red cells (upper arrow). The underlying elastica is fragmented and separated by collagen fibers and traces of AMP. There is a hyalinized scar in the muscularis (lower arrow). (Heart N 2 circumflex branch left coronary artery Movat × 120 AFIP Neg 66-4064.)

Bottom left. This is damaged subendocardial arteriole. The essel is surrounded by scar tissue nd it wall is thickened by scar tissue and AMP reducing the lumen to a crescent-shaped slit. The overlying endocardium (not show) is also scarred. (Heart No. 2 subendocardium left entricular apex, Movat, × 140 AFIP Neg. 66-7386.)

Bottom right. This is segment of a coronary ein containing an orga izing thrombus that obstructed the lumen t a slightly lower level. There is an agonal extravasation t the point of ttachment (arrow). The adventitia and surrounding pericardial f t is infiltrated by AMP. (Heart N 2 pericardium posterior ll of right entricle Mov t × 50 AFIP Neg 66-7387.)

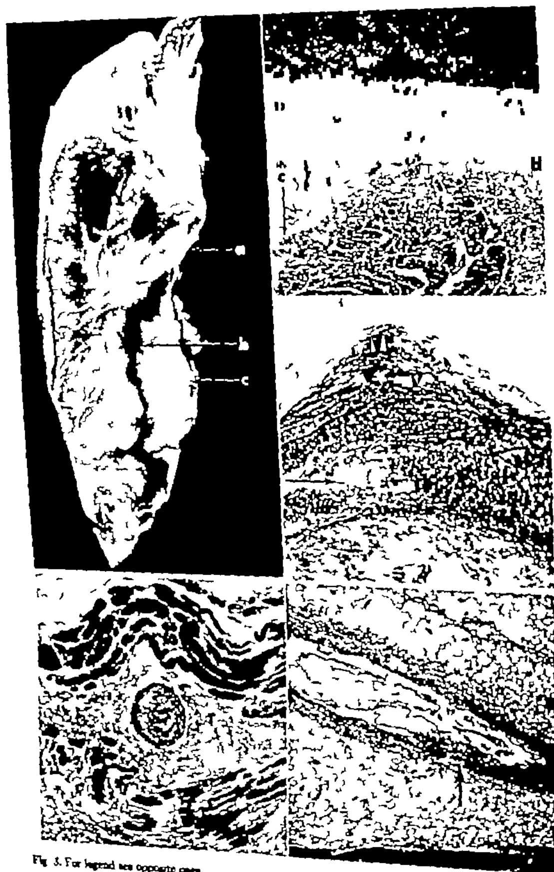


Fig. 3. For legend see opposite page.

COLOR PLATE I

Top left A 27 year-old Rwanda male agricultural worker died after a 12 day illness which originated with d spnea nd hemoptysis nd was followed by congestiv heart failure Two month previously he had had short episode of fever nd chest pai The photograph shows soft yellow matrix adherent t the posterior wall of the left entricle A la er of fibrin overs the lesion which fills the recess behind the posterior mitral leaflet extends down the posterior wall nd encroaches on the endocardium of the septum. It engulf the free margin of the posterior leaflet the leaflet hordae tendineae and the posterior papillary muscle This is one of the three sites commonl l ed in EMF and in this heart it was the only gross lesion The other sites commonly in l ed are the left nd right entricular apices. Some heart ha e all 3 sites involved, others ha only 1 or 2 sites This bulky mass is an organizing matrix of mucin covered by fibrin (see middle right picture). It can be distinguished from the usual intracardiac mural thrombus, because the latter is composed of interlacing trand of fibr w th enmeshed erythrocytes and leukocytes. This lesion is 1.0 cm. thick and the left entricle is 1 3 m thick. N te that the chordae tendineae are not shortened or thickened the leaflet are not fused t the ommissures and the atrial endocardium is smooth and glistening There is no MacCallum patch (Heart N 1 m tr l al X 0 6 AFIP Neg 66-7378.)

Top righ Although the endocardial lesion in heart No. 1 was the only prominent gros feature, there were ma y m roscopic foci of m ocardial degeneration This section through the pex of the right ventricle show 2 ircumscribed punched-out areas of muscle fiber degeneration These are composed of reticulum fibers, capillaries, l mphocytes, and few macrophages containing lipofuscin Strands of collagen stained yellow with saffron are beginning t form Many of these lesions surround or are adjacent t damaged arterioles nd are probabl microscopic inf rcts. The majority occur in the inner third of the myocardium but they are also seen he middle nd outer thirds, including the muscle layer immediately beneath the epicardium (See also Fig 2) (Heart N 1 ight entricular apex Movat X 42 AFIP Neg 66-1428.)

Middle left A 28-year-old Rwanda woman wif of an agricultural worker died after 5-week illness that beg w th "fever was followed by dyspnea on effort cough, and palpitations, and was later complicated by severe dyspnea nd hemoptysis. The only gross cardiac lesion was the yellowish-gray matrix adherent t the posterior wall of the left entricle (arrow). It fills the recess behind the posterior mitral leaflet pushing it forward Not that the posterior commissure is normal nd the posterior wall of the left atrium is not scarred. The erior leaflet is slightly thickened along ts line of closure. Microscopically there were focal incre ses of acid mucopol saccharide in the alve substance (Heart N 3 mitral alve, X 0.5 AFIP Neg 66-7379)

Middle right This is horizontal section t the level of the arrow in the middle left picture Surface fibrin ha enmeshed the hordae tendineae (top arrow) nd blends into an nderlying layer of organizing mucin ( ) The latter is permeated by capillaries and contains mesenchymal cells, Anitschkow myocytes, nd mixture of hronic inflammatory ells including lymphocytes, plasma cells nd ma t cells. Many of the mesenchymal cells are wollen with mucin There is thin layer of scar tissue t the level of the tip of the lowest arrow Here he collagen bundles are swollen they ha lost their fine fibrillations and they are separated by acid mucopolysac haride The arterioles in the underlying myocardium are thick w lled and ha e partially obliterated lumens I addition there is marked perivascular nd interstitial fibrosis. (Heart No. 3 endocardium of posterior w ll of left entricle Movat X 20 AFIP Neg 66-1455)

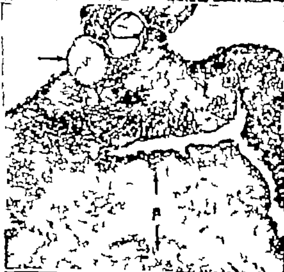
Bottom left A 23- ar-old Rw nda woman died after 5 months of dyspnea nd progressiv sw lling of her abdomen and legs. At necrops her heart contained a small scar t the tip of the right ventricular apex and 2 lesions of the left entricle show here Both are yellowish gray homogeneous, nd adherent t the mural endocardium The lesion of the posterior w ll fills the recess behind the posterior mitral leaflet nd has enmeshed the free margin of the leaflet nd he ttached chordae tendineae The lesion extends behind the anterior m tral leaflet and encroaches on the septal endocardium (see Fig 2) and dow the posterior wall but stops abruptly t the base of the posterior papillary muscle There is 1.2-cm. skip area between this and the apical lesion The pic l lesion has maximum thickness of 1.5 cm (Heart N 4 mitral val e, X 0.5 AFIP Neg 66-7380.)

Bottom right A 12 year-old Rw nda girl died fter 4 y ar illness haracterized by congestiv failure and chronic pericardial effusions The pex of the right entricle w severely inv ol ed (see Fig 9), and there w slight endocardial hickening of the left entricle This arteriole is situated in the wall of the left entricle just bene th the base of the posterior papillary muscle It wall is thickened by AMP stellat and round mesenchymal cells, nd Anitschkow myocytes The endothelium is swollen and its lumen is virtually obliterated. Only fragment of surviving smooth muscle that are seen as scattered pink fibers, are evident The wall of the large coronary essels as well as those of many intramuscular vessels contained AMP In some areas the AMP was organizing, but in others, it had progressed t scar In addition there were numerous tellate myocardial scars in the walls of the lef nd right entricles (Heart No. 9 left entricle Movat, X 200, AFIP Neg. 66-1063)













epicardial vessels, including the extramural coronary vessels, were not otherwise remarkable. Atherosclerosis was minimal. The main coronary arteries contained an occasional small flat atheroma but none of these was ulcerated or calcified or in any way compromised the lumen.

MYOCARDIUM. None of the 16 hearts was excessively hypertrophied. In those with right ventricular fibrosis, the pulmonary conus was dilated and hypertrophied (Fig 8 middle left, Fig 9 bottom left, Fig 11 middle left). Pointed tracts of scar tissue extended from the thickened endocardial plaques into the myocardium. These penetrating tracts were most prominent in the hearts with thick endocardial scars and in patients with long clinical histories (Fig 12 right). There were no other gross lesions of the myocardium.

ENDOCARDIUM. There was a recurring pattern of gross endocardial lesions. The right and left ventricular apices and the posterior wall of the left ventricle were repeatedly involved. Fourteen of the 16 hearts had fibrosis of the right ventricle. In some it was only slight (see Fig 10 top left), but in each the thickest portion of the scar was at the apex and tapered toward the tricuspid ring (Fig 5 middle left, Fig 8 top right, Fig 9 middle left, Fig 10 bottom right). In 9 hearts the fibrosis encased the papillary muscles and thus held the tricuspid leaflets rigid, which allowed free atrioventricular communication in life. The tricuspid leaflets themselves, however, were not scarred. Even in those hearts with severe right ventricular fibrosis (dilatation of the tricuspid ring and atrialization of the right ventricle) the tricuspid leaflets remained thin, translucent, and unscarred. In 1 heart there were fibrotic nodules around the chordae tendineae (Fig 6) but there were no other lesions of the tricuspid chordae. In contrast to the dominant apical lesion of the right ventricle, there were 2 characteristic endocardial lesions of the left ventricle—one on the posterior wall and the other at the apex. The lesions on the posterior wall involved the endocardium of the recess behind the posterior mitral leaflet, the chordae attached to the posterior mitral leaflet (Fig 1 top left), and a small portion of the endocardium of the outflow tract (Fig 2 top left). The apical lesions were thickest right at the apex and tapered sharply toward the endocardium of the septum, the outflow areas, and the inflow tract, which ended at the base of the posterior papillary muscles (Color Plate I bottom left, Fig 2 top left and Fig 8 bottom left). In the hearts with the 2 lesions of the left ventricle, a zone of uninvolved or less severely involved endocardium separated them (Color Plate I bottom left, Fig 2 top left, Fig 5 top left, Fig 8 bottom left). When the clinical course was short, the endocardial lesions were soft, bulky, and grayish green (Color Plate I top middle and bottom left, Fig 1 top left and Fig 3 top left). In those with longer histories, the endocardial lesions were hard and white (Fig 7 top left, Fig 8 bottom left, Fig 10 top right, and Fig 11 bottom right). In no heart did the scar at the left apex contract or distort the contour of the left ventricle. In 9 of the 12 hearts with lesions on the posterior wall, the posterior mitral leaflet was contracted or bound to the posterior wall (Fig 5 top left, Fig 8 bottom left and right, and Fig 11 middle right). Neither the anterior mitral leaflet (Fig 4 bottom) nor the cusps of the pulmonary and aortic valves were involved. A layer of fibrin covered the endocardial lesions in 6 hearts (Nos. 1, 2, 3, 4, 5, and 7). This layer could be distinguished from the usual antemortem thrombi because it was a soft, homogeneous, butterlike matrix that was grayish green.

THROMBI AND EMBOLI. There were antemortem thrombi in the right atrial appendages of four hearts (Nos. 6, 8, 12, and 14). These thrombi differed in no way from the thrombi found in hearts failing from other causes. These hearts had markedly dilated right atria, tricuspid dilatation, and scarring of the right ventricle. Two patients died of embolic accidents. One (No. 8) had a massive pulmonary infarction caused by 2 emboli that originated in the right atrial appendage. The embolization may have been triggered by an arrhythmia because there was atrial tachycardia with complete A-V dissociation on the day of death. The other patient (No. 5) died suddenly when a large ball of fibrin dislodged from the left ventric-

COLOR PLATE II

Top left. A 6-year-old Rwanda boy died after a 1 month illness characterized by severe dyspnea and swelling of the legs and abdomen. At autopsy the heart was globular and there was minimal scarring of the right ventricular apex (Fig. 10, top left), but there were dense endocardial scars in the left ventricle (Fig. 10, top right). One scar was on the posterior wall of the left ventricle behind the posterior leaflet of the mitral valve and the other at the left ventricular apex. This photomicrograph is from a section of left ventricular endocardium taken through the junction of the scar and normal endocardium (tip of arrow a, Fig. 10, top right). The uppermost layer (A) is a mixture of collagen and elastic fibers separated by AMP that contains a few stellate mesenchymal cells. In the more active zone (B), the collagen bundles (long vertical arrow) and fine elastic fibers are surrounded and separated by AMP and some of the tissue is smudged and colored red by fibrin (horizontal arrow). The 2 short vertical arrows point out 2 of the many mesenchymal cells that contain AMP. Beneath this explosive zone is a layer of AMP and stellate mesenchymal cells surrounding and infiltrating the innermost myocardial fibers. (Heart No. 10, endocardium of left ventricle. Movat, × 145. AFIP Neg. 66-1458.)

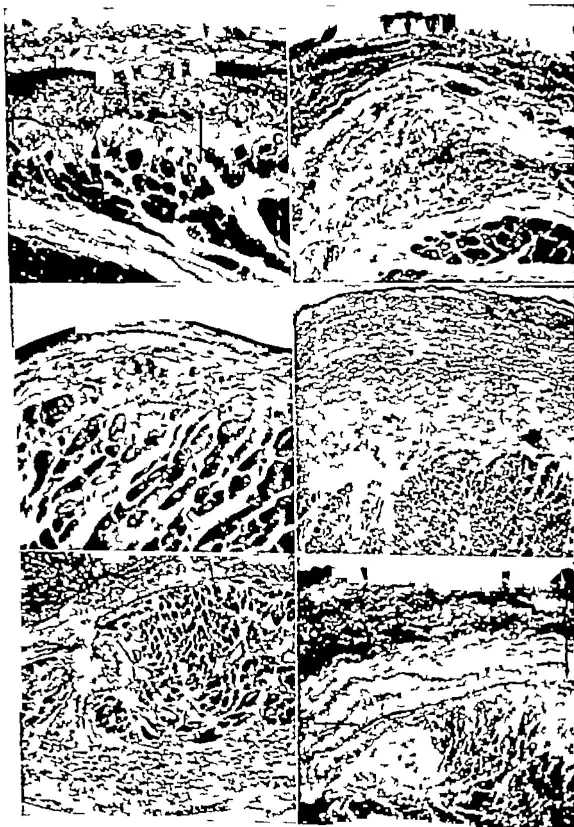
Top right. This section was taken through the area at the tip of arrow b, Fig. 10, top right. The superficial portion of the scar (collagen, elastica, and smooth muscle) is compact and quiescent, but below this there is an explosive lesion characterized by a central focus of degenerating collagen and swelling of the surrounding tissue. The central collagen fibers are swollen and stained orange red. Mesenchymal cells containing blue-stained AMP surround the central area of necrosis. The underlying muscle is edematous but otherwise unremarkable. (Heart No. 10, endocardium of the left ventricular apex. Movat, × 145. AFIP Neg. 66-1456.)

Middle left. A 40-year-old Rwanda man died after an illness of 2½ years. At the onset he had features of pericarditis and pleurisy; later he had severe congestive failure. At autopsy there was a hard, white endocardial scar extending from the recess behind the posterior mitral leaflet down the inflow tract to the apex. In the right ventricle there were nodular scars on 2 chordae tendineae, and there was a patchy milky discoloration of the inflow endocardium that merged with scattered focal scars (see Figs. 6 and 7). This section is from the right ventricular apex, where there was slight gross endocardial thickening. As seen here, the endocardium is thickened by a mixture of elastic and collagen fibers focally disrupted by a central zone of collagen degeneration. AMP has accumulated in the endocardium and in the interstices of the underlying myocardium. (Heart No. 7, right ventricular apex. Movat, × 265. AFIP Neg. 66-7381.)

Middle right. This is from a section of the left atrium just above the posterior mitral leaflet, at b in Fig. 7, top left. The endocardium is thickened and the collagen and elastica are separated by AMP. At the arrow tips deep in the thickened endocardium there are discrete foci of collagen necrosis. Fig. 7, middle right, is an enlargement of the largest necrotic focus. (Heart No. 7, left atrium. Movat, × 70. AFIP Neg. 66-7382.)

Bottom left. A 26-year-old Rwanda woman died of pulmonary infarction after a 15 month illness characterized by intermittent congestive heart failure. At autopsy the right ventricular apex was obliterated by scar tissue, the posterior wall of the left ventricle was scarred, which fixed and partially obliterated the posterior mitral leaflet and its chordae tendineae, and there was a broad scar at the left ventricular apex; see Fig. 8. A grayish-red friable thrombus filled the apex of the right atrial appendage. This section is taken through the tip of the right atrial appendage. The thrombus (above) rests on an endocardium that is slightly thickened by collagen and elastic fibers. The epicardium below is also thickened by scar tissue. A large amount of AMP separates the muscle fibers. (Heart No. 8, right atrial appendage. Movat, × 105. AFIP Neg. 66-7383.)

Bottom right. A 10-year-old Rwanda boy died after 1 year of progressive dyspnea and congestive heart failure. At autopsy there was fibrosis and contraction of the right ventricular apex, fibrosis behind the posterior mitral leaflet, and fibrosis of the left ventricular apex. This is a photomicrograph of the left apical scar, an enlargement of a portion of Fig. 5, top right. There is a mixture of collagen, elastica, and smooth muscle (layer A) fixed to the original endocardium, which is here seen as discontinuous strands of collagen and elastica (arrow B). Although this surface scar is compact and "inactive," there is a focus of collagen degeneration in the myocardium. The collagen bundles are swollen, they are separated by AMP, they have a distinct tinctorial change and have lost their fibrillations. There are a few mesenchymal cells in the mucinous matrix. The other tissue at the right has similar changes. (Heart No. 6, left ventricular apex. Movat, × 105. AFIP Neg. 66-4062.)



obstructed the aorta at the renal arteries (Fig 4 top and middle left)

WEIGHT The hearts of the adults with EMF weighed from 240 to 420 grams and averaged 358 grams. In the entire group the heart weights varied from 0.4 to 1.3 per cent of body weight. None of the hearts was greatly enlarged Even the heaviest heart (420 grams) was not in the weight range of those hearts with so-called idiopathic hypertrophy There was no correlation between the degree of cardiomegaly and age sex duration of symptoms, or pattern of lesions, but there was a tendency for the heavier hearts (in proportion to body weight) to have thinner endocardial scars.

Fundamentals of clinical cardiology

Acute pulmonary embolism

I Review*

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To be or not to be? To beget or not to beget? To operate or not to operate? These are questions requiring answers when acute pulmonary embolism is under consideration But the *possibility of pulmonary* embolism is not considered in approximately one half of the patients who subsequently are shown at necropsy to have naked-eye evidence of this disorder [1,2] The percentages of patients who survive unrecognized pulmonary embolism and of those misdiagnosed as having this disorder are unknown Nonetheless acute pulmonary embolism is probably the commonest lethal pulmonary disease in the United States today the primary cause of at least 50 000 fatalities annually and a contributing cause to the death of several times that number of additional patients. There is also evidence that the introduction of additional diagnostic aids and energetic treatment have not as yet prevented an increase in the incidence of and deaths from acute pulmonary embolism

It is therefore appposite and timely to review this subject with the purpose of determining what can be done to increase diagnostic accuracy and therapeutic success. Pulmonary embolism cannot be adequately reviewed in isolation because it is in the middle and the most serious component of a triad *with venous thrombosis* first and pulmonary infarction third The last two are caused by their immediate predecessors but the first two do not necessarily beget a successor This review will therefore also touch on venous thrombosis and pulmonary infarction

Incidence

The incidence of pulmonary embolism is unknown Pulmonary arterial webs a residual sign of pulmonary embolism have been found in 9 5 per cent of necropsies.[3] If pulmonary embolism at times leaves no residual signs as has been documented under experimental conditions it must occur at least once in more than 10 per cent of the population Indeed there are some who believe that pulmonary embolism is continually taking place especially after major operations, but that the emboli are quickly lysed by defensive pulmonary mechanisms.[4] It is very likely that many

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pulmonary emboli if not most are silent. The lung parenchyma has no pain fibers and therefore, unless appreciable hemodynamic changes occur or pulmonary infarction follows, even a widespread awareness by physicians of the magnitude of this problem will not result in clinical recognization of most pulmonary emboli.

Breckbridge and Ratnoff[7] reviewed a medical examiner's record in order to determine the least incidence of lethal pulmonary embolism in presumably previously healthy persons. They found an incidence of 2 7 per million males, 3 8 per million females, and 18 per million pregnancies. The true incidence is obviously higher because not all persons who die suddenly are examined by the medical examiner

Castleman and his associates found that pulmonary embolism was responsible for almost one of every seven deaths, the commonest cause of death in their hospital. Morrel Truelove, and Barr[4] found an impressive rise in the incidence of pulmonary embolism there being five times as many cases in 1961 as in 1952 They quote the British Ministry of Health which reported that the risk of embolism becomes appreciable after age 30 and climbs with age especially after 50 It found the incidence approximately 5 per 1,000 at age 50 in medical patients and 2.5 per thousand in surgical patients. The incidence rose steeply to 22 per thousand at age 80 in the medical group and 13 per thousand in the surgical group.

Pulmonary embolism commonly thought to be practically nonexistent in children was found in nearly one per cent of 10 000 necropsies done on children under the age of 16 Half of these were in infants under one year of age Practically all of these children had an underlying serious illness, the commonest being congenital heart disease Dehydration also appeared to be an important factor In contrast to the situation in adults the site of primary thrombus formation when identifiable was usually in large vessels such as intracranial sinuses (25 per cent) intra-abdominal veins (20 per cent) superior vena cava (15 per cent) right side of the heart (15 per cent) and pulmonary artery (15 per cent) The emboli were therefore frequently large In spite of this, the diagnosis was suspected on clinical grounds in only 1 of the 73 patients who had pulmonary emboli frequently multiple, at necropsy

Predisposing factors

The following clinical states are clearly associated with an increased incidence of acute pulmonary embolism

1 Age This association has already been noted About 90 per cent of fatal pulmonary emboli occur after the age of 50[3]

2 Cardiac disorders Over 100 years ago Cruveilhier found that pulmonary embolism occurred most commonly in persons with cardiac disorders. His observations have been abundantly confirmed In some series heart disease is present in as high as two thirds of patients with pulmonary embolism[11,12] Congestive heart failure is an additional predisposing factor Pulmonary emboli are found at necropsy in about half of all patients whose deaths were preceded by congestive heart failure. Atrial fibrillation is also an important additional predisposing factor

3 The postoperative period In some series as high as one third of all instances of acute pulmonary embolism occur in this period The most common operations predisposing to pulmonary embolism are cardiac, biliary gastric, and prostatic operations and operations on the pelvis and lower extremities.

4 Major trauma particularly fracture of the pelvis and lower extremities These states are associated with the highest incidence of pulmonary embolism.[12]

5 Neoplasms. These are also associated with a high incidence of pulmonary embolism and also with unusual sites of thrombophlebitis both disorders tend to be resistant to anticoagulation therapy

6 Blood dyscrasias These include leukemia, polycythemia, sickle cell anemia, and sickle cell trait.

7 Pregnancy and the early postpartum period The incidence of pulmonary embolism in young pregnant women is about 7 times that of an age-matched group of nonpregnant women. During delivery and the immediate postpartum period the release into the circulation of amniotic fluid and other products of conception may result in a syndrome in which both a clotting and a bleeding tendency coexist,

appropriately called a consumption coagulopathy[11]

The possibility that thromboembolism may be related to the use of contraceptive pills is under active investigation There is at this time no statistical proof of such an association although the clinical settings of a few sporadic cases suggest a possible cause-and-effect relationship There is evidence suggesting changes in clotting and fibrinolytic properties of blood produced by contraceptive pills [14] but the relation between these changes and thromboembolism is not clear

8 *Infection and malnutrition* These are particularly common predisposing factors in children (usually with heart disease)[16]

9 *Obesity* This factor appears to increase the risk of venous thrombosis formation most strikingly in young patients in whom pulmonary embolism has been thought to be uncommon[1]

10 *Strenuous effort*[16]

11 *Portacaval shunt surgery*[7] It has recently been reported that there is an unusually high incidence of both silent and clinically manifest pulmonary emboli in patients who have had a shunt created between the portal vein and the inferior vena cava. It remains to be established whether this incidence is greater than might be encountered in a similar group of chronically and critically ill patients in whom no such iatrogenic shunt exists.

12 *Immobility* This is common to most of the other predisposing causes. Relative immobility is particularly likely to be a factor in presumably healthy persons who sit for prolonged periods of time such as in an aeroplane and particularly when they are tall and habitually cross their legs.

Thrombophlebitis should be regarded as a source of rather than a factor predisposing to the development of acute pulmonary embolism

Of the predisposing factors listed above the most frequent ones are congestive heart failure particularly if atrial fibrillation is present and recent surgery or trauma The incidence varies so greatly in different series, depending upon the factors which determine patient selection and whether the statistics are based on clinical or necropsy data that a quantitative estimate of the various factors would be of questionable value.

It is important to re-emphasize, however that pulmonary embolism does occur and may even be massive and fatal in apparently healthy young subjects. Among younger patients, massive emboli are more likely to occur in pregnant women and in male subjects with a past history of an apparently insignificant genital or rectal infection Other predisposing factors appear to be obesity sitting for prolonged periods of time with the knees flexed prolonged standing without walking sudden unaccustomed physical exertion and varicosities—particularly with a history of previous thrombophlebitis.

Pathogenesis

A foreign substance may become impacted temporarily or permanently anywhere in the pulmonary arterial tree Rare causes are air fat and atherosclerotic and calcareous particles. This discussion will be limited to thrombosis which is almost always the cause.

Thrombi are found when diligently sought at necropsy in the deep veins of the lower extremities in from 60 to 85 per cent of subjects with pulmonary emboli.[1,16] Thrombi may be found in veins adjacent to an operative site and in the right atrium in subjects with congestive failure and/or atrial fibrillation. It is customary to assume that a pulmonary embolus arose from a thrombus found in the deep veins of the lower extremities. Angrist[17] re-emphasized that a thrombus cannot be in two places at the same time. To identify the source of an embolus, one must demonstrate a loss of a pre-existing zone of a thrombus or intimal changes characteristic of a detached thrombus. Furthermore these lesions must be proximal to a complete occlusion if present Frequently thrombophlebitis is bilateral and a thrombus arises more commonly from the extremity that appears innocent clinically[11]

Just what triggers the formation of a thrombus is as yet not established It is generally agreed that stasis[17] alone is insufficient to cause venous thrombosis. At the present time there is a tendency to regard venous (red) thrombus as ...

initially to activation of the intrinsic coagulation mechanism producing a transient local hypercoagulable state[illegible] and to regard arterial (white) thrombosis as due initially to exposure of collagen to the blood stream.[illegible] These conclusions are implicit in the design of many of the experiments. Just what triggers the activation of the intrinsic coagulation mechanism is not clear.

Soaps of long-chain saturated fatty acids or adenosine diphosphate (ADP) which they may generate, produce thrombi whether injected into an artery or vein.[illegible] The arterial thrombi lodge at the bifurcation of vessels and the venous ones behind venous valves. In these experiments, thrombi tend to grow by impaction of a detached thrombus upon an attached proximal one.[illegible] Postoperative increased platelet adhesiveness was demonstrated[illegible] before the role of ADP was known.[illegible] It has been shown that increased adhesiveness and aggregating tendency of platelets are present when ADP is added to blood taken from patients with clinical signs of venous thrombosis or established tendency to thrombotic episodes.[illegible] But ADP is probably not the only or final common pathway forming platelet aggregation.[illegible]

Pulmonary embolism is produced by partial or total detachment of the thrombus. It has been suggested that trauma, or force during exertion (e.g. defecation) may dislodge the thrombus. Embolism may occur without prodromes, sometimes during sleep.[illegible] Others have suggested that the blood current detaches or fractures the thrombus which has partly shrunken. It appears unlikely that venous flow could generate sufficient force to accomplish this effect. One of us (L. A. S.) has observed in the bat repeated violent contractions of increasing amplitude in the vasculature proximal to and at the site of a thrombus which keeps rocking the thrombus back and forth until a portion or all of it is detached. These motions cannot be blocked by denervation of the vasculature and therefore appear to be produced by a local mechanism.

Once the thrombus is released and reaches the lung (probably within 7 to 10 seconds) hemodynamic and gross anatomic changes do not necessarily follow. Gibbon, Hopkinson and Churchill[illegible] showed over 30 years ago that occlusion of the pulmonary artery may be innocuous. When clots are injected into the pulmonary artery no circulatory or respiratory changes occur even when they are impacted at the bifurcation of the main pulmonary artery or its branches. The clot reduces significantly in size within four days, becomes flat against the vessel wall, endothelializes at the point of attachment by outgrowths from the vasa vasorum, and within 28 days the vascular tree is normal. It is therefore possible that embolization occurs invariably following all surgical procedures but that the natural shrinking of a clot, enhanced by fibrinolysis and the blood current, all favor gradual absorption of the clot.[illegible] This concept is supported by the finding that injection of platelet agglutinates at weekly intervals up to 43 weeks in dogs fails at necropsy to show any pathologic changes in the pulmonary vasculature. Symptomatic pulmonary embolism apparently occurred experimentally only if intervals between embolization and the sizes overcame the capacity of the lung to dispose of them. Pre-existing lung disease may tip the odds in favor of clinical signs of embolism. Old clots also favor clinical signs because shrinkage is slowed or does not occur and they are or may be resistant to thrombolysis.[illegible]

Even the largest emboli may not cause pulmonary infarction. Pulmonary infarction will not occur unless there is previous obstruction of the pulmonary artery or pulmonary venous hypertension.[illegible]

These experimental findings and clinical manifestations may be more readily and effectively evaluated and understood if we first review briefly data relating lung structure and function. With this background, a clearer insight into the mechanisms producing the variable clinical picture of pulmonary embolism may be obtained.

Normal pulmonary structural and functional relationships

There is a close anatomic association between the branches of the pulmonary artery and those of the bronchial tree.[illegible] The proximity between pulmonary arterial vessel and bronchial tree is maintained to the most distal vascular branch that can

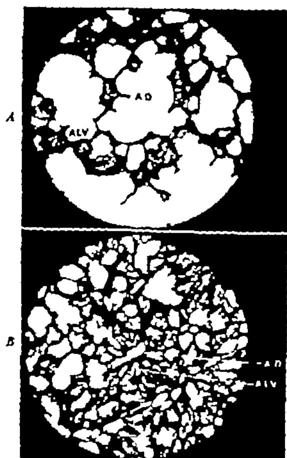


Fig. 1. The microscopic appearance of an alveolar duct (*AD*) with its surrounding alveoli (*ALV*). *A*. The alveolar duct with its satellite alveoli widely dilated. *B*. The results of alveolar duct constriction. As a result of the muscle which surrounds the openings of the alveoli, constriction of the alveolar duct musculature results in marked *narrowing of the* duct itself with almost complete obliteration of the alveoli which arise from it. (Reprinted through the courtesy of the authors and the publishers from Nadel, J. A., Colebatch, H. J. A., and Olsen, C. R.: J. Appl. Physiol. 19:387, 1964.)

be recognized as an arteriole by virtue of its smooth muscle content. The pulmonary capillaries arise from this terminal arteriole which is about 50μ in diameter. They branch off at a 90 degree angle from the arteriole forming morphologically a unique vascular pattern.[34] The bronchial airway branch which correspond to the terminal arteriole and which lies in close proximity to it, is a respiratory bronchiole, the first portion of the airway to contain gas exchange units, alveoli. As the airway progresses distally from this point it divides into alveolar ducts from which numbers of alveoli arise. The alveolar duct contains strands of muscle fibers which surround the openings of the alveoli so that alveolar duct constriction results in pulling in and near or complete collapse of its alveoli (Fig. 1). The smallest functional unit of the lung is most likely made up of the terminal pulmonary arteriole together with its respiratory bronchiole.[35] It contains about 100 alveolar ducts, each giving rise to about 20 alveoli so that the entire unit contains about 2,000 alveoli. Adult human lungs contain about 150,000 such units making a total of about 300 million alveoli. In contrast to the close anatomic proximity of the pulmonary artery and its bronchus, the branches of the pulmonary veins tend to run in the lobular septae at a considerable distance from both the corresponding pulmonary artery and bronchus or bronchiole. The anatomic arrangement outlined above probably provides the mechanism for the regional regulation of ventilation to perfusion which normally results in a *minimum of wasted ventilation* (little alveolar dead space) and a minimum of wasted perfusion (little or no admixture of venous blood that has passed through capillaries not exposed to well ventilated alveoli). Both the pulmonary arteriole and its respiratory bronchiole are within the actual substance of the lung parenchyma, completely surrounded by alveoli. They are therefore effectively located to sense changes in respiratory gas concentrations. A reduction in local blood flow (as from a small pulmonary embolus) is quickly followed by a drop in the carbon dioxide concentration of the neighboring airway. This localized hypocapnia results in constriction of the respiratory bronchioles and alveolar ducts which compensatorily diminishes ventilation to an area of poorly perfused lung tissue requiring little or no ventilation.[36] It has not as yet been established whether the hypocapnia acts directly on bronchiolar smooth muscle or whether its effect is humorally mediated by local release of some substance such as histamine. Similarly, if ventilation is reduced to a small area of lung tissue as by microatelectasis, the resultant decrease in oxygen concentration in the airway is sensed by the adjacent pulmonary arteriole. Arteriolar spasm oc-

curs with deflection of pulmonary blood away from the poorly ventilated lung tissue. Until recently it was generally believed that the low oxygen concentration acted directly on the arterioles. Recent studies suggest that the vasospastic effect of airway hypoxia and/or pulmonary embolism may be humorally mediated possibly by a substance produced by the alveolar cell.[24] The morphologic and physiologic arrangement outlined above appears to provide the lungs with a sensitive regulatory mechanism for matching regional air flow and blood flow and thereby avoiding or minimizing the gas exchange problems of ventilation perfusion imbalance.

A clear concept of the relationship between the pulmonary and bronchial circulations is also essential to an understanding of the sequellae of pulmonary embolism. In the human lung the bronchial circulation supplies arterial blood to the airways down to the terminal bronchiole.[22,27] Beyond the terminal bronchiole beginning with the respiratory bronchiole, the airways are nourished by the pulmonary arterioles as well as by oxygen in the airways themselves. The bronchial arteries also supply the vasa vasorum of the pulmonary arteries, the blood vessels of the interlobular septae, and those of the visceral pleura.[27] Communications normally exist between the bronchial and pulmonary arterial vessels at the level of the precapillary. These bronchopulmonary anastomoses do not ordinarily exceed 40μ in diameter but they are capable of enlarging to 200 or more μ in diameter and of generating muscle tissue in their walls in the presence of diminished pulmonary blood flow or bronchial inflammatory disease.[27] The direction of flow is, of course from the high pressure bronchial to the low pressure pulmonary vessel. In addition to these bronchopulmonary communications there are also other potential anastomoses between the systemic arterial and pulmonary arterial systems by way of the intercostal arteries and the vessels in and around the diaphragm.[27]

Although it has not been established with certainty it appears likely that potential communications also exist at the precapillary level between the pulmonary arterioles and pulmonary venules.[22]

Pathophysiologic manifestations of pulmonary embolism

1 Wheezing The occurrence of wheezing in patients who have sustained a pulmonary embolus has been observed frequently. Until recently the pathophysiology underlying the bronchoconstriction whose audible counterpart is the course inspiratory and expiratory wheeze was obscure. Serotonin,[24] released from the platelet embolus and/or from platelets adhering to the embolus, produces generalized constriction of the larger branches of the bronchial tree.[23] Platelet aggregation is facilitated by thrombin. If thrombin activity is inhibited by the administration of heparin platelet aggregation is retarded and bronchoconstriction and wheezing following pulmonary embolization are either prevented or ameliorated.[23] Heparin must be administered in large doses to block thrombin activity. The intravenous administration of 15 000 units (150 mg.) of aqueous heparin has been reported to result in prompt amelioration of wheezing in patients who have just suffered a pulmonary embolus.[17] Heparin itself has no antiserotonin activity.[24] Serotonin induced bronchoconstriction appeared to be a reasonable explanation for the dyspnea which almost invariably accompanied a clinically apparent pulmonary embolus. However more recent studies have demonstrated that serotonin affects primarily the larger airway (not the bronchioles) and although the wheezing produced by the *movement of air through these narrowed tubes* may be quite spectacular the actual resistance to air flow rarely increases more than twofold.[28] Since the subjective sensation of breathlessness rarely occurs with airway obstruction until the resistance is increased at least fourfold there is serious doubt that bronchoconstriction is the primary etiologic factor in the dyspnea of pulmonary embolization. The prompt administration of heparin following recognition of a pulmonary embolic episode is certainly rational both to prevent propagation of the clot in the pulmonary circulation and to inhibit thrombus formation at the primary site but, in the light of our present knowledge its usefulness appears to be primarily prophylactic rather than therapeutic since it is doubtful

that the anti-serotonin effects described above substantially alter the course or outcome of the embolic episode.

2. Increase in pulmonary vascular resistance and pulmonary blood pressure. Many investigators have reported that experimental pulmonary embolization results in an increase in pulmonary vascular resistance and in pulmonary hypertension out of proportion to the volume of the vascular bed occluded.[39-43] This phenomenon is difficult to demonstrate with large emboli which occlude one or more lobar or segmental arteries[41] but has been observed fairly uniformly following microembolization of the pulmonary arterial tree with particles which are trapped in the precapillary arteriolar bed.[42-44] The onset of pulmonary hypertension and pulmonary arteriolar spasm is fairly rapid (within minutes) but it is transient (less than an hour in most experiments).[44] It has even been demonstrated that generalized pulmonary arteriolar spasm is evoked by microembolization of a lobar artery whose mouth has been occluded by a distended balloon. The hemodynamic response to mircoembolization of an already occluded vasculature cannot be attributed to purely mechanical factors. A neural reflex involving the autonomic nervous system was originally postulated[41] but the response is not greatly altered by vagotomy nor cervical sympathectomy nor by the administration of drugs which block either the parasympathetic or sympathetic systems.[42,47,48] It is now generally recognized that the pulmonary vasospastic response is mediated by a humoral factor which has not been identified as yet.[47] Since the pulmonary arteriolar vasospasm is most readily induced by emboli which are trapped in the precapillary arterioles, it seems likely that the humoral substance may be the same one which results in arteriolar spasm in response to airway hypoxia. The stimulus causing its release is conjectural. It may be mechanical irritation of the vessel wall by the particles or possibly hypoxia of the arteriolar and alveolar cells secondary to the occlusion. It has recently been suggested that distention of pulmonary arterial walls without occlusion of the lumen of the vessel results in generalized pulmonary arteriolar and pulmonary venous spasm and opening of pulmonary arteriovenous communications.[49] These observations have not as yet been confirmed. Other investigators have isolated a humoral substance from hypoxic lung which induces transient generalized pulmonary arteriolar spasm. Evidence for such a humoral substance has been obtained by cross circulation experiments, by injection of extracts of hypoxic lung tissue[50] and by injection of the saline perfusate of hypoxic alveoli.[50] In any case, the production of pulmonary hypertension by microembolization is quite transient and is seen only under highly artificial experimental conditions that do not correspond to the usual clinical acute pulmonary embolism. The vasospastic response of the pulmonary arteriolar bed is probably an experimental artifact related to disturbance of the normal ventilation perfusion regulatory apparatus. In a classical study of the mechanism of death in *recurrent* pulmonary embolism Gorham demonstrated convincingly that death could rarely if ever be attributed to pulmonary embolism unless 60 percent or more of the vascular bed had been mechanically occluded.[44,45,52] Pulmonary vasospasm associated with experimental pulmonary embolism has attracted much investigative interest and its further clarification will probably give us much greater insight into normal and pathologic pulmonary physiology, but it seems unlikely that this hemodynamic reaction plays a significant role in acute pulmonary embolism as it is usually encountered clinically.

3. Gradient of carbon dioxide between arterial blood and alveolar air. The concentration of carbon dioxide in alveolar air under normal circumstances is identical with that in systemic arterial blood. Immediately following experimental pulmonary embolization in animals, the alveolar carbon dioxide concentration is considerably less than that in arterial blood because the air coming from the unperfused alveoli contains no carbon dioxide and therefore dilutes the carbon dioxide content of the alveolar air coming from the nonembolized areas of lung (Fig. 2).[53] The carbon dioxide gradient between arterial blood and alveolar air can be used to calculate the volume of lung tissue that is ventilated but not

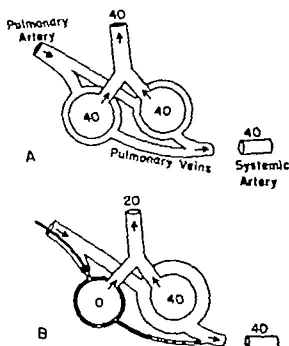


Fig. 2 Diagrammatic illustration of the bases for the gradient in carbon dioxide between arterial blood and alveolar air following an acute pulmonary embolus. *A* The normal state when all areas of both lungs are normally perfused so that the blood leaving the pulmonary capillary bed and reaching the systemic arteries has a partial pressure of carbon dioxide of 40 mm. Hg which is identical with that in the alveolar air to which the pulmonary capillary blood has been exposed. *B* The theoretical result of occlusion of one of the pulmonary arteries with no change in ventilation to the lung. The partial pressure of carbon dioxide in the alveoli of this lung immediately drops to zero due to the absence of perfusion. The partial pressure of CO_2 in the contralateral lung remains at 40 due to compensatory hyperventilation. As a result the partial pressure of CO_2 in the arterial blood is unchanged (40 mm. Hg) but the partial pressure of CO in the alveolar air is reduced to 20 mm. Hg since it is the average of that coming from the perfused lung and that coming from the unperfused lung. This description is based on the assumption that ventilation to the unperfused lung is maintained at 50 per cent of total ventilation. (Reprinted through the courtesy of the authors and publishers from Robin, E. D., Forkner, C. E., J., Bromberg, B. A., Croteau, J. R., and Travis, D. M. New England J. Med. 262:283 1960).

perfused (alveolar dead space) i.e. the embolized portion of the lungs. Robin and his associates[33,34] and others[35] have demonstrated that the measurement of this arterial alveolar carbon dioxide gradient may be useful in the recognition of acute pulmonary embolism in man. The usefulness of this test is limited by the fact that shortly after the acute embolic episode in both animals and man the magnitude of the gradient begins to decrease fairly rapidly.[33] The decrease can be attributed to the fact that compensatory mechanisms are invoked and ventilation is shifted away from the nonperfused lung tissue resulting in a reduction of the alveolar dead space created by the embolus.[35,36,37] This ventilation shift is almost certainly related to airway hypocapnia which induces bronchiolar and alveolar duct constriction.[32,37,38] The administration of gas enriched with carbon dioxide to the non perfused lung tissue prevents the local diminution in ventilation.[32,35] This ventilatory shift which follows both experimental and clinical pulmonary embolism is desirable in that it tends to reduce alveolar dead space (wasted ventilation) and to restore normal regional ventilation perfusion relationships. Although the measurement of the arterial-alveolar carbon dioxide gradient has been useful in the detection of acute pulmonary embolism the test may yield spuriously positive results in the presence of tachypnea or parenchymal lung disease.[15] The test has generally been replaced by two other newer diagnostic techniques, lung scanning and pulmonary angiography.

4 Atelectasis Roentgenographic evidence of "platelike" atelectasis is sometimes seen following acute pulmonary embolism. This subgross atelectasis may be related to the ventilatory shift mentioned above. Another possible explanation for its occurrence can be found in the observation that several hours following a pulmonary embolus the lung tissue distal to the occluded vessel has a decreased concentration of surfactant probably secondary to bronchiolar and alveolar cell hypoxia since surfactant is produced in either the alveolar or bronchiolar cells. This substance, which lowers surface tension at the pulmonary gas-liquid interface, the area of the alveolar-capillary membrane, is essential to maintain the physical stability of the lung, i.e. to prevent smaller alveoli with greater surface tension from collapsing into larger alveoli with lesser surface tension. The combination of alveolar duct constriction which decreases alveolar volume together

with reduced surfactant activity can be expected to promote collapse of alveoli in the embolized portion of the lung. In most cases, the atelectasis which results is probably microscopic and transient since surfactant levels usually return to normal within 24 hours. Sutnick and Soloff have shown that the mean minimal surface tension of human lungs with pulmonary emboli was 6.9 ± 3.8 dynes per centimeter and with pulmonary infarction 19.1 ± 4.7 dynes per centimeter compared to a normal of 5.5 ± 1 dynes per centimeter.[illegible] In experimentally produced infarction in the dog, the C^{14} phospholipid converted from C^{14} palmitic acid was 23,000 counts per minute per gram in the infarcted tissue compared to 733,000 in the normal lung tissue.[illegible] These findings support the concept that surfactant synthesis is dependent upon adequate pulmonary circulation and that the interruption of pulmonary blood flow is responsible for a fall in metabolic activity of the alveolar epithelial cells and diminished surfactant production which predisposes to atelectasis. If underlying pulmonary disease or infection is present, surfactant production is further compromised. In the presence of pulmonary infarction, atelectasis may be more gross and persistent but, in our experience, persistent segmental or lobar atelectasis is uncommon following acute pulmonary embolism.

5. *Anastomoses between bronchial and pulmonary arteries.* The anstomoses which normally exist at the precapillary level between the bronchial and pulmonary arteries are capable of enormous proliferation following acute pulmonary embolism.[illegible] An increase in blood flow through these channels which brings systemic arterial blood into the pulmonary vascular bed probably begins within two hours following acute pulmonary embolism. Over a period of several weeks, these anastomotic vessels enlarge rapidly, lose the morphologic characteristics of capillaries, and begin to resemble muscular arterioles.[illegible] Eventually the volume of blood flow provided by these collateral vessels to the lung tissue distal to the embolus may exceed the normal pulmonary blood flow.[illegible] In animals several weeks following transection of a main pulmonary artery, all of the vessels distal to the transection are patent and contain systemic arterial blood and the volume of blood flow through the lung is normal although the pulmonary arterial inflow has been entirely eliminated.[illegible] Since the bronchial arteries supply the vasa vasorum of the pulmonary arteries, another potential source of collateral blood flow may result from growth of bronchial vessels into the organizing embolus with recanalization of the occluded pulmonary artery.[illegible] This rich collateral network is probably responsible for the fact that pulmonary infarction rarely follows pulmonary embolism if the lung is normal and is uncommon even if there is underlying lung disease or passive vascular congestion. On the other hand, it has been suggested by other observers that the bronchial flow may be responsible for the phenomenon that is unique to the lung, namely, that an infarct, when it does occur, is uniformly hemorrhagic. These observers feel that the pulmonary vascular bed, normally a low pressure system, does not tolerate the sudden influx of blood delivered at systemic pressures.[2] With regard to respiratory gas exchange, bronchial blood may effectively dissipate carbon dioxide as it traverses the pulmonary capillary bed, but it is unlikely to pick up any additional oxygen since its hemoglobin is already nearly fully saturated except in the patient (uncommonly encountered) who has persistent arterial oxygen unsaturation following acute pulmonary embolism. Since carbon dioxide dissipation is rarely impaired even by recurrent pulmonary emboli, the bronchial collateral blood flow serves only to preserve the viability of the distal respiratory apparatus, the respiratory ducts and alveoli which are normally dependent on pulmonary blood flow.[illegible]

6. *Pulmonary infarction.* With regard to the pulmonary parenchyma, probably the commonest course of events following embolic occlusion of a major branch of the pulmonary artery (lobar or segmental) is transient or incomplete *infarction*. The alveoli become full of red blood cells which have leaked through the capillary walls but the alveolar-capillary membrane, at least when studied by light microscopy, is intact. The cells are rapidly removed and the lung parenchyma then appears rela

tively normal The process of exudation and resorption of red cells is complete within several days. The usual clinical manifestation is an evanescent infiltrate on the chest x ray [64] The source of the red cells is probably backflow from the pulmonary venous system which may be aggravated by reflex or humoral pulmonary venous spasm that has been observed following experimental pulmonary embolism or experimental distention of a pulmonary artery without lumenal occlusion.[77, 80] Generalized pulmonary edema is occasionally seen after experimental or clinical acute pulmonary embolism [64] It is difficult to explain on any other basis than pulmonary venous constriction

In a small percentage of cases of acute pulmonary embolism (probably less than 10 per cent) a true pulmonary infarction occurs.[62] Experimentally pulmonary infarction is almost impossible to produce unless pulmonary embolism is accompanied by passive vascular congestion or pulmonary infection [81, 67] As a general rule the same is true for the intact human being since pulmonary infarction is most commonly encountered in patients with underlying primary heart disease. The infarct is always hemorrhagic the alveolar walls are necrotic, and healing is by fibrosis.[9] Healing is accompanied by an ingrowth of systemic vessels which eventually communicate with the pulmonary arteriolar bed [77] These systemic vessels arise from the bronchial system which supplies the visceral pleura from the intercostal arteries which supply the parietal pleura, and from arteries which nourish the diaphragm These potential systemic pulmonary communications are so rich that parietal pleurectomy has been suggested as an effective technique for revascularizing the pulmonary capillary bed in patients with cyanotic congenital heart disease with low pulmonary blood flow

7 *Pulmonocoronary artery reflex* It was once postulated that impaction of an embolus in the pulmonary circulation instituted a reflex (pulmonocoronary) which reduced coronary blood flow There is no experimental or clinical evidence for the existence of such a reflex.[71, 72] Direct observation of the human heart during stimulation and stretching of the pulmonary arteries has not revealed any cardiac or coronary artery changes.[73] Recent animal studies have demonstrated an increase in coronary blood flow following acute pulmonary embolism The increased coronary blood flow was related to arterial hypoxemia and could be relieved by oxygen administration.

8 *Spontaneous thrombolysis* We have already referred to the frequency and rapidity of lysis of pulmonary emboli [7, 14] The human body contains an efficient thrombolytic system [75] From the therapeutic standpoint it is worth re-emphasizing that freshly formed thrombi are readily lysed while older ones which have begun to organize at their site of origin prior to dislodgement are more resistant.[75] Pulmonary infection and passive congestion also appear to impair the endogenous thrombolytic mechanism [64] Embolectomy may therefore be required more often in patients with these complications than in patients with similar sized emboli who are free of heart disease and infection

9 *Pulmonary functional changes* Although a multitude of changes in pulmonary function occur following acute pulmonary embolism, they are usually not diagnostic. The patient suffering from a recent embolic episode is frequently too ill to undergo the rigors of extensive pulmonary function studies. Most of the data concerning changes in pulmonary function following acute pulmonary embolism have been obtained from studies on animals, and can readily be understood in relation to the physiologic abnormalities discussed above.

TACHYPNEA The most obvious and most consistent pulmonary functional change is tachypnea.[36] Its etiology is obscure since a reduction in lung compliance the change in the mechanical properties of the lungs which normally produces an increased respiratory rate is rarely of sufficient magnitude to account for the striking rise in respiratory rate which is usually seen.

CHANGES IN THE MECHANICAL BEHAVIOR OF THE LUNGS A more easily explained finding is an increase in airway resistance which may be attributed at least partially to serotonin induced constriction of the large airways [36] If this were the primary factor responsible for the increase in air

way resistance, it should be accompanied by a decrease in anatomic dead space (due to narrowing of the large airway). Experimental studies suggest that major airway constriction is only a contributory factor to the increase in airway resistance.[33] Jaffe and Figley[44] recently demonstrated in animals that airway resistance could be increased by infusion of serotonin or histamine or by pulmonary embolization with autologous clot. Bronchographic studies during the experiments showed constriction of the large airway following the administration of the pharmacologic agents but not after embolization. The primary factor is probably constriction of respiratory bronchioles and alveolar ducts which results in alveolar collapse (Fig. 1), a reduction in lung compliance (due to loss of lung volume) and an increase in anatomic dead space due to secondary dilatation of the larger airways proximal to the constricted respiratory bronchioles and alveolar ducts.[7, 71]

INCREASED ALVEOLAR VENTILATION. Although the increase in the volume of minute ventilation that follows acute pulmonary embolism is due primarily to an increase in rate rather than an increase in tidal volume, the absolute level of alveolar ventilation is usually elevated with a resultant decrease in the partial pressure of carbon dioxide in the arterial blood.[44, 45]

INCREASED ALVEOLAR DEAD SPACE. The increase in alveolar dead space, which is reflected by the carbon dioxide gradient between arterial blood and alveolar air, is due to the ventilation of unperfused alveoli. It is usually quite transient as compensatory mechanisms are quickly invoked to shift ventilation to better perfused areas of lung tissue.

INCREASED ALVEOLAR AIR–ARTERIAL BLOOD OXYGEN GRADIENT. More persistent than the CO_2 change is an increase in the oxygen gradient between the alveolar air and arterial blood. It results from the failure of complete correction of the ventilation-perfusion imbalance produced by the embolic episode and reflects an increase in venous admixture due most likely to relative overperfusion of normally ventilated alveoli.

ARTERIAL OXYGEN UNSATURATION. One of the most intriguing and perplexing changes that may follow acute pulmonary embolism is arterial oxygen unsaturation.[41, 43, 44, 34, 57] It is seen fairly consistently in experimental embolization in animals, particularly microembolization, but also occurs in human subjects following spontaneous embolic episodes.[44] Eleven possible mechanisms have been invoked to explain systemic arterial desaturation: (1) perfusion of underventilated alveoli secondary to tachypnea;[41] (2) perfusion of unventilated alveoli secondary to generalized alveolar duct constriction;[71] (3) overperfusion of normally ventilated alveoli in areas to which blood has been shunted;[44] (4) atelectasis;[44, 72] (5) alveolar hypoventilation;[43, 44] (6) increased blood velocity through pulmonary capillaries;[43] (7) pulmonary edema;[44] (8) anatomic shunting through pulmonary arteriovenous communications;[44, 73] (9) an anatomic shunting through the foramen ovale;[75] (10) anatomic shunting through communications between the bronchial and pulmonary venous systems;[45] (11) impaired diffusion.[43, 4]

The evidence for several of these mechanisms is quite flimsy and they can probably be disregarded as important factors. These include alveolar hypoventilation, increased blood velocity through pulmonary capillaries, pulmonary edema, and impaired diffusion due to loss of alveolar-capillary surface area. These pathophysiologic phenomena may occur occasionally but are insufficient to account for the frequency or severity of desaturation observed. Evidence for the other seven possible factors is more substantial and, under different circumstances, experimental or spontaneous, they all may contribute to the arterial unsaturation. In experimental microembolization, precapillary potential anastomoses between the pulmonary arterioles and venules probably become functional and create an anatomic shunt.[43] In such experiments, the emboli must be quite small to lodge distal to the site of the potential anastomoses. In all likelihood in spontaneous human embolism, the occlusion is usually proximal to these precapillary vessels and no such shunt occurs. When arterial oxygen unsaturation is encountered in patients, it is most likely to be due to one or more of the following four factors: (1) the perfusion of underventilated alveoli that results from

tachypnea with small tidal volumes (2) perfusion of underventilated alveoli secondary to alveolar duct constriction (3) relative overperfusion of areas of lung tissue to which blood has been shunted which would normally pass through the occluded vessel (ventilation is not comensurately increased to these overperfused areas) (4) microatelectasis secondary to loss of surfactant activity and alveolar duct constriction

The functional importance of these four mechanisms is supported by the observation that the systemic arterial unsaturation can frequently be corrected by instituting controlled ventilation with air at slow respiratory rates and increased tidal volumes.[a] This breathing pattern without oxygen-enriched gas mixture, would tend to correct venous admixture due to any of these four factors but not the venous admixture of an anatomic shunt.

In the presence of a large or massive pulmonary embolism arterial unsaturation uncorrected by oxygen administration may occur suggesting the presence of anatomic shunting The most likely explanation for this phenomenon lies in the normal communications between the bronchial and pulmonary venous circulation Ordinarily about 50 per cent of the bronchial circulation (about one per cent of the cardiac output) empties into the pulmonary venous system constituting an insignificant right to-left shunt. In the presence of acute right ventricular failure, the elevated venous pressure may be transmitted back through the azygous system and the bronchial veins to the pulmonary veins, resulting in a much larger right to left shunt. Some support for this thesis has been obtained by the recent observation that arterial unsaturation can be related to the elevation in right atrial pressure.[10] Under these circumstances, the anatomic shunt might be through the bronchial veins or through the patent foramen ovale which exists in about 20 per cent of normal subjects.

Finally large or massive pulmonary *embolism in the clinical sense may anatomi*cally be due to a massive pulmonary embolus or to several less-than-massive emboli or even to a less-than-massive embolus complicating pre-existing pulmonary disease and dysfunction

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The treatment of cardiogenic shock
Part II The use of pressor agents in the treatment of cardiogenic shock

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The most widely employed pharmacologic agents for the treatment of shock due to acute myocardial infarction have been the so-called vasopressors. This category includes drugs such as methoxamine or angiotensin II which have purely peripheral vasoconstrictive (-adrenergic) effects, and little or no direct cardiac or β-adrenergic effect as well as those with both inotropic and peripheral vasoconstrictive actions. Drugs with combined effects, such as norepinephrine and metaraminol have been used most commonly and have been until recently almost routine therapeutic agents in the treatment of acute myocardial infarction with shock. Agents which have solely inotropic effects on the myocardium (beta stimulators) i.e isoproterenol and mephentermine, and little or no pressor effect on the peripheral circulation may also cause elevation of arterial pressure in certain instances of shock these will not be considered directly in this article.

From both theoretic considerations and limited clinical observations, the reasonable conclusion seems to be that in the treatment of shock due to acute myocardial infarction, agents with combined inotropic and peripheral vasoconstrictive effects are preferable to those with solely peripheral vasoconstrictive effects. More recently the traditional use of the agents norepinephrine and metaraminol in acute myocardial infarction with shock has been questioned vasodilators or purely inotropic agents have been suggested as replacements. It is the purpose of this article to review some of the pertinent evidence concerning this and to assess the usefulness of vasopressor agents in this syndrome.

Both experimental and clinical hemodynamic studies have indicated that, in myocardial infarction with shock, there is a precipitous fall of cardiac output and by definition arterial pressure. Experimental studies have also shown early fall of coronary flow despite coronary vasodilatation, although this parameter has not been adequately determined in human beings with acute myocardial infarction. These hemodynamic derangements are progressive for the fall of coronary perfusion pressure leads to further fall of coronary flow and hence deterioration of cardiac function, the development of serious arrhythmias, an increased fall of cardiac output, circulatory deterioration, and progressive acidosis. Systemic vascular resistance has varied considerably in patients with acute myocardial infarction

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with shock some patients demonstrate a considerable increase some little change despite a fall of cardiac output and others, a reduction of systemic vascular resistance

To what extent are these hemodynamic abnormalities relieved by the use of nor epinephrine or metaraminol What have been the clinical benefits and hazards with their use? Are there agents presently available which have been proved superior?

Discussion

Norepinephrine and metaraminol have the important effect of increasing the depressed arterial pressure in acute myocardial infarction with shock this increases the perfusion pressure to vital areas of the circulation including the heart and the brain although other areas of the circulation perhaps immediately less crucial may be rendered ischemic Coronary perfusion pressure is an important determinant of coronary flow particularly when there is acute myocardial ischemia, which generally results in significant coronary vasodilatation A coronary circulation that is supplied by diminished perfusion pressure, as in shock may show more increase of flow with increments of arterial pressure than a circulation in which the perfusion pressure is not initially depressed Increase of the diminished coronary flow of acute myocardial infarction improves the function of the heart and lessens its susceptibility to fatal arrhythmias diminution of coronary flow has the opposite effects. The inotropic effects of these agents increase the reduced cardiac output of acute myocardial infarction with shock. Therefore it can be appreciated that both effects are rational in attempting to correct the observed hemodynamic alterations in acute myocardial infarction with shock.

The extent to which these agents have been clinically effective has been studied by several investigators. Unfortunately despite the frequency of clinical use of these agents, there are few detailed hemodynamic observations. In 258 patients in 17 reported series in which norepinephrine was used for the treatment of acute myocardial infarction with shock an effective pressor response was noted in about 77 per cent (range 45 to 100 per cent) and there was relief of the clinical manifestations of shock in 51 per cent (range 14 to 100 per cent) These series showed a 60 per cent mortality rate (range 14 to 100 per cent) as compared to a very high mortality rate in untreated shock (range 80 to 100 per cent) In 3 different series of patients with acute myocardial infarction and shock there were 23 in whom determinations of cardiac output were performed Apparently norepinephrine produced a significant increment of cardiac output in 14 patients there was no change in 4 of them there was some diminution of cardiac output in 5 others. Of course, the considerable variability of the reported results may be due not only to intrinsic differences among the patients, but also to the fact that treatment may have been administered in various stages of the syndrome and that varying criteria for the definition of shock may have been employed Any therapy that is administered very early in the course of shock may be expected to be more effective than it is when given later in the course after there has been prolonged circulatory deterioration and its attendant depression of cardiac function acidosis, and perhaps irreversible hemodynamic alterations. Similarly when criteria for the definition of shock are loosely defined response to treatment can be expected to be more striking than when more rigid criteria are employed

There is some evidence of a preliminary nature from a small series of cases, that vasopressor drugs may produce a greater increase of cardiac output in patients with initially low cardiac output and elevated systemic vascular resistance, than in the patients with initially low or normal systemic vascular resistance and only moderately reduced cardiac output This should be confirmed by a larger series of cases The optimum level of arterial pressure that is to be sought with pressor agents has not been defined Diaphoresis, tachycardia and ischemic chest pain are commonly noted when these agents are given too rapidly a rapid increment of left ventricular oxygen requirement is probably the cause One study has suggested that when the arterial pressure rises to about 100 mm Hg systolic or 90 mm Hg mean, cardiac output may be increased but further elevation of arterial pressure may

produce no additional increment of cardiac output. This, too requires further confirmation and study It has not been clarified whether or not previously hypertensive patients require a higher optimum arterial pressure level in the treatment of shock than previously normotensive patients. It is probable that careful subdivision of patients with acute myocardial infarction and shock into homogeneous hemodynamic subgroups will define more precisely those individuals who may respond predictably and beneficially to the vasopressor agents or to other types of drugs. This will require rapid preferably computerized on-line determinations of hemodynamic and metabolic alterations, and their response to treatment

Arguments against the use of vasopressors in the treatment of acute myocardial infarction with shock have been put forth on several bases. An obvious criticism of their use is their relative ineffectiveness or only transient efficacy as evidenced by the continuing high mortality rate in this syndrome despite the vigorous use of these agents. The available data relevant to this have been reviewed previously Although there are differences of opinion concerning the degree of efficacy of vasopressor agents, the weight of the evidence indicates that in most (but not all) series, lives seem to have been saved There are many instances in which an immediate and dramatic pressor effect is obtained in severe hypotension with ultimate survival of the patient Certainly mortality figures in several reports in which vasopressor therapy has been used are lower than in reports of untreated shock, where the mortality rate approaches 100 per cent if strict criteria are used for its definition Whether or not any other types of agents have given superior results or are inherently more rational in the treatment of this syndrome is a key question

Other arguments against the use of vasopressors in the treatment of acute myocardial infarction with shock, rest on 2 main suppositions. One is that cardiogenic shock is characterized by a common hemodynamic pattern consisting of intense systemic vasoconstriction which result in organ ischemia, acidosis, and irreversible circulatory deterioration. Thus, it is reasoned that agents which cause further vasoconstriction with attendant organ ischemia cannot be helpful under these circumstances and that more rational therapy would require the substitution of vasodilators, possibly with plasma expansion. However as noted previously careful analysis of hemodynamic alterations in both experimental and acute myocardial infarction with shock in man reveals a variety of hemodynamic patterns, and disproportionate increase of systemic vascular resistance is by no means universally present. In fact about one half of all patients with acute myocardial infarction and shock who have had detailed hemodynamic studies demonstrate normal or reduced systemic vascular resistance despite a considerable reduction of cardiac output. It is not necessarily valid to transfer conclusions that are based on experimental or clinical hemorrhagic or septic shock to clinical acute myocardial infarction with shock Vasodilators which may further depress coronary perfusion pressure (even though flow in other organs may be increased) may be tolerated well if there is little or no myocardial ischemia but when the left ventricle is acutely ischemic and the coronary perfusion pressure is already low a further decrease of perfusion pressure which is an important determinant of coronary flow may result in further deterioration of ventricular function and serious arrhythmias.

The harmful effects of increasing the pressure work of the ischemic left ventricle with vasopressors have also been stressed. Even though this is an undeniable effect of this class of drugs, any attempt to raise the arterial (coronary perfusion) pressure from shock levels, and thereby restore the hemodynamic alterations toward normal will be associated with increased load on the left ventricle and an increase in its oxygen requirement. Clinically patients with acute myocardial infarction and shock whose arterial pressures remain at shock levels almost invariably succumb while the survivors are almost always among those whose arterial pressures show some elevation with therapy It should be realized that norepinephrine and metaraminol also possess inotropic effects which serve to increase the

contractile force of the ventricles. In addition a marked increment of coronary flow with probable left ventricular functional improvement has been associated with the increase of coronary perfusion pressure. Our own studies have indicated that a mechanically induced rise in aortic pressure and systemic vascular resistance (by balloon obstruction of the abdominal aorta) in experimental acute myocardial infarction with shock was associated with a sharp increase in coronary flow, an increase in cardiac output and left ventricular mechanical efficiency, and a decrease in left ventricular excess lactate production. The left atrial pressure did not rise above normal limits. These results support the view that the level of arterial pressure and coronary flow are important in determining left ventricular response to an increased resistance and that beneficial effects on left ventricular function may be obtained when aortic pressure is raised from shock levels and coronary flow is thereby increased despite the concomitant increase of left ventricular work. Many other studies of the effects on left ventricular function of increased left ventricular outflow resistance have been performed with conclusions that vary somewhat but these have been mainly in experimental and clinical settings without acute myocardial infarction and severe hypotension. Adaptive mechanisms which permit the left ventricle to respond to an increase of outflow resistance with enhanced myocardial contractility have been described.

Despite the less than desirable efficacy of the conventionally used vasopressor agents and certain theoretic objections to their use, no other class of pharmacologic agents has been established as superior. Other types of agents will be discussed in separate articles in this series but clinical experience with the use of vasodilators (e.g., phenoxybenzamine) with or without plasma expanders (e.g., dextran) or inotropic agents (e.g., isoproterenol or dopamine) has not been extensive enough to clearly define the hazards or advantages to patients with acute myocardial infarction and shock. Each has certain theoretic beneficial effects but each one has undesirable effects as well. The hazard of vasodilators with their attendant reduction of coronary perfusion pressure have been mentioned. Plasma expanders may cause a sudden and dangerous elevation of plasma volume in an individual with acute myocardial infarction even though the central venous pressure is monitored carefully because the elevation of left atrial pressure to pulmonary edema levels may develop while the right atrial pressure is still normal or just slightly elevated. Isoproterenol is a potent chronotropic agent, particularly when the left ventricle is acutely ischemic, and it may increase the oxygen requirement of the left ventricle without a concomitant increase of coronary perfusion pressure and flow. This may be manifested by ischemic pain and an increase of left ventricular excess lactate, the product of anaerobic myocardial metabolism.

Conclusions

No agent has been clearly established either clinically or experimentally as superior to norepinephrine or metaraminol in the treatment of acute myocardial infarction with shock, so there is no definite indication at present for abandoning their use. A variety of pharmacologic agents, perhaps in combination, require further investigation with detailed measurement of the sequential hemodynamic, metabolic, and clinical effects they produce. On the basis of this information it may be possible to establish hemodynamic and clinical groupings of patients with predictable responses to different types of therapeutic agents.

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Annotations

Atrial function following cardioversion

Atrial fibrillation constitutes a hazard to the patient for 2 main reasons. First, it is associated with a high incidence of systemic embolization (about 25 per cent in the series has been reported by Goldman. Second, the loss of effective left atrial contraction results in several undesirable hemodynamic changes. The atrial boost to ventricular filling is particularly important when cardiac reserve is impaired, such as occurs in the diseased heart. Loss of atrial contraction can lead to a reduction of up to 40 per cent in the cardiac output. The loss of the valve-closing action of atrial systole is another, although it is a relatively minor disadvantage.[3]

The introduction of the technique of D.C. conversion provided a simple and safe method of converting atrial fibrillation to sinus rhythm.

Braunwald[5] and Logan and associates[6] showed by means of pre- and postconversion right and left heart catheterization that the return of a normal P wave on the ECG is not necessarily accompanied by a return of atrial systole. Furthermore, right atrial systole may return before left atrial systole. This was particularly common if the atrial fibrillation was due to disease which affected mainly the left side of the heart, such as mitral valve disease. This observation has very important practical implications since the beneficial effects of conversion to sinus rhythm are based on the assumption that mechanical systole of both atria returns in a synchronous manner with the return of normal sinus rhythm on the electrocardiogram.

We studied left atrial systole by means of the apex displacement cardiogram. The method[7] is sensitive enough to detect even the small displacement of the apex due to normal, left atrial systole. We detected right atrial systole by studying the jugular venous pulse. This enabled us to time the return of right and left atrial systole by daily recordings which could not be done by catheter studies. The results are reported in detail elsewhere. Fourteen patients who suffered from various diseases that caused atrial fibrillation were studied. The majority of patients were afflicted by chronic rheumatic mitral valve disease. The results of this study showed that left atrial systole may not return for days or weeks after the return of electrical atrial activity on the ECG. In patients with atrial fibrillation due to disease of the left side of the heart, right atrial activity returned promptly whereas the left atrium did not contract for several days or weeks after conversion. The average time for return of left atrial contraction was 3 to 4 days. In one patient, who had had aortic and mitral valve replacement for chronic rheumatic disease, left atrial systole was not detected for the 3 weeks her heart was in sinus rhythm before relapsing into atrial fibrillation. These observations have provided a clue to 2 otherwise inexplicable, clinical problems.

First, pulmonary edema occurs in a small number of patients whose hearts are successfully converted. We believe that this is related to the enhanced output of the right ventricle due to return of right atrial systole which tends, in the absence of a concomitant increase in the left heart output, to flood the lungs. The occurrence of actual pulmonary edema depends on factors, such as pulmonary capillary permeability and mean left atrial pressure that are favorable to its formation. In most patients, the atrial fibrillation is a result of chronic mitral disease and in such cases, the pulmonary capillary membrane is much thicker than normal; this tends to prevent alveolar edema formation in the lungs. This fact would partly explain the rarity of this complication, which usually is detectable only radiologically. The report of a case of a woman who developed pulmonary edema after spontaneous reversion to sinus rhythm[10] would support the view that this complication is dependent on hemodynamic factors, rather than on myocardial injury due to the electrical discharge.

The observation that the left atrium may not contract, even though there is a normal P wave on the ECG, raises the concept of "left atrial failure." This concept was first introduced in 1944.[11] The authors reported the case of 2 young pregnant women with mitral stenosis who died from acute pulmonary edema while their hearts were still in sinus rhythm. The findings at autopsy showed hypertrophy and fibrosis of the left atrial muscle. It is obvious that the sudden failure of left atrial contraction in a person with mitral stenosis would lead to a fall in the cardiac output consequent upon impaired ventricular filling and a rise in pulmonary venous pressure due to a rise in mean left atrial pressure. This rise in pulmonary venous pressure would tend to cause pulmonary edema; this tendency is further aggravated by the continued presence of right atrial systole which tends to flood the lungs as has been suggested above.

Our studies support the thesis that left atrial failure can occur despite the presence of normal

sinus rhythm demonstrated on the ECG. We believe that this loss of left atrial systole may often be responsible for the sudden deterioration or death in the absence of obvious cause, in patients not only with mitral valve disease but also with other left-sided lesions such as, aortic valve disease, systemic hypertension and coronary artery disease, in whom myocardial reserve is impaired to the point that an effective left atrial contraction becomes of critical importance in maintaining the efficiency of the left ventricle.

The second complication we have encountered in 3 patients is that of systemic embolization which occurs several days after cardioversion. The fact that left atrial systole can be delayed for several days provides a ready explanation for this phenomenon. The therapeutic implications of these findings are that anticoagulants and therapy for heart failure should not be discontinued until obvious evidence of left atrial contraction is present.

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Hypertension and nephrosclerosis: A reappraisal and a new theory of renal ischemia

Although the kidney is strongly implicated in many of the clinical settings of abnormally elevated blood pressure and experimental correlations abound, there still are many reasons for confusion about its role in the over all spectrum of hypertensive disorders. In recent years there has been many speculations about multifactorial causes of hypertension and it has become fashionable to speak of hypertension as a mosaic. As the mosaic has become more Byzantine it has *been increasingly difficult to perceive* a unifying pathogenetic pattern. The mosaic approach has the virtue of emphasizing that in chronic, sustained, or fixed hypertension a number of mechanisms may be contributing to the elevated blood pressure. However it has somewhat clouded the issue of what causes the hypertension initially. Whereas a number of relatively rare humoral and nervous mechanisms may initiate hypertension the important problem of the initiation of the common form of human hypertension persists. The role of the kidney remains problematical although there is good precedent for regarding it as the prime mover in the hypertensive sequence. This confusion is based on clinical and pathologic difficulties in relating the kidney to essential hypertension. Early in the course kidney function is normal and, in later or established hypertension renin levels *in the peripheral blood* usually are not elevated. The pathologic examination of the kidney usually discloses scars in the *surface* renal cortex associated with thickening of intrarenal arterioles, that is most commonly fibrous intimal *proliferation*.

An observation which was made in adult human autopsy material showed a statistically close correlation between the occurrence of such scars and the presence of complicated lesions of atherosclerosis of the aorta at or above the renal artery orifices, and suggested that platelet microembolism as pathogenetic mechanism in the development of the renal scars. The mechanism is analogous to the occurrence of transient cerebral ischemic attacks in individuals who have complicated atherosclerotic lesions of the large neck arteries. Subsequent experiments which were designed to test this hypothesis

ha shown in the rabbit that the surface renal cortex is peculiarly sensitive to embolic damage. When formed masses of thrombus are used, infarcts result MgAl wire (98 per cent Mg) contained in catheter in which holes ha been cut is inserted into the thoracic aorta. Platelet masses form on the holes and are pparently repeatedly dislodged due to the electrolytic disintegration of the wire. Such masses cause areas of trophy characterized by atrophic tubules and *shrunken glomeruli, along the renal* cortical surface. Below these lesions, the arteriolar essels show massive intimal proliferation which is considered to be response to the lodgement of emboli and analogous t the lesions that are seen in lung vessels in conditions of repeated or prolonged microembolism from deep ein thrombosis of the legs, or after experimental embolization.[16] Distal t the vessel narrowing caused by this proliferation, the smooth muscle cells of the media undergo remarkable transformation to cells with numerous cytoplasmic granules which stain in similar way t those of the conventional juxtaglomerular apparatus.[11] This hange persists for some weeks but then declines nd in 6 months, is usually absent. At this time, normal granularity of the juxtaglomerular apparatuses has been re-established in the unaffected, normal (nonatrophic) areas from which it has been absent earlier and time when the arterioles of the trophic areas had been granular.

These morphologic findings suggest that the kidney through the renin-angiotensin system, is important *in initiating the hypertension, but that* thereafter some other mechanism comes into play to sustain t. This is consistent with observations on Goldblatt type renal hypertension in the rabbit, in which it was found that nephrectomy cured the hypertension only if performed before 7 weeks had elapsed. There is of course nothing new in the suggestion that the renal mechanism is primary and some other mechanism perhaps neurogenic one, sustains the hypertension. This dual mechanism was proposed by Ogden in 1947[13] and has been supported by other experimental evidence.[14] More recently Koletsky and associates[16] hav show that chronic infusion of angiotensin in rats can lead to sustained hypertension, which persists after the *angiotensin is stopped. The* sustaining mechanism may well be the one proposed by McCubbin.[17]

At 6 months the rabbit kidneys show lesions that closely resemble those of the human granular kidney of essential hypertension.

Thus, an experimental model of sustained hypertension, in which lesions similar to those of the human disease are produced, has resulted from an pproach based on the proposition that the kidney lesions are caused by embolism from complicated aortic atherosclerosis.

The experimental situation is clearly analogous to that of human essential hypertension, in that similar kidney lesion is present and normal juxtaglomerular granularity suggests that the plasma *renin is normal or not elevated in the chronic part* of the experiment, as is the case of fixed hypertension in humans.[18]

Obviously various manipulations of the experimental model will ha to be carried out to elucidate these relationships further. Since this theory is contradictory t the idea, idely held that the renal lesion is itself econdary t the raised pressure some explanation will ha *t be found for the fact that* benign nephrosclerosis is seen in 75 per cent of an elderly (erage age 64)[8] autopsy population. At present, one could say that, in some cases, intrarenal essel narrowing may be severe enough to cause trophy but not enought to stimulate increased renin production. This is made more likely *by these observ tions, in which the trophy and* hypergranularity of essels occu in the same renal territory (i.e. distal to the essel narrowing, that is brought about by embolism).

The concept, that hypertension is initiated by ischemic kidney damage which is brought about by thrombotic emboli from aortic therosclerosis would seem to be supported by many of the epidemiologic aspects of hypertension. The age distribution, its initial fluctuant nature,[19] its racial distribution[20] and hereditary aspects[21] are more easily explained by renal microembolism than, for example, by the neurogenic or endocrine theories. The concept also returns the kidney to the central position in hypertension that Goldblatt has always claimed for it. The pathogenesis of many of the scarred kidneys that are encountered at autopsy is also made more clear.

One of the current clinical concerns is the question of the importance and treatment of renal artery stenosis.[22] It is becoming increasingly apparent that the results of therapy are not as good as one would expect if the renal artery narrowing provided the *main timulus to hypertension. This theory provides* an explanation for the possibility of good result if the stenosis is very recent, and of the probability of poor result in long-standing disease. If the kidney is alread damaged by microembolism, the hypertension ma well be permanent or fixed, and the correction of the renal artery stenosis or the removal of the kidney should ha no, or only temporary effect. It provides insight into the observation that results are better in fibromuscular disease of the renal arteries, disease usually seen in young omen.

Other diseases in which platelet microembolism may play part should be investigated.

This theory has some therapeutic implications. Since it changes the traditional emphasis on hypertension as disease which facilitates the developmen of atherosclerosis, it suggests that in mild hypertension there is little to be gained by treatment. It offers hope for amelioration from study of antiplatelet clumping agents.

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Unusual sign of perforation of a pacemaker catheter

It is w ll know that pacemaker catheters introduced transvenou ly may perforate i to the pericardial a ity. The perforation may be accompanied by signs of cardiac tamponade but more often it is discovered through loss of pacing[1-4] by roentgenographic demonstration of hange in the position of the tip of the catheter or as an incidental finding t surgery The patient may complain of chest pain nd friction rub may be heard but the perforation may lso be entirely free of symptoms or signs.

A ery peculiar rly sign of pacemaker catheter perforation was recently noted in this department.

A 61-year-old man was admitted for total A V block with multiple Adams-Stokes attacks. A No. 5 pacemaker catheter with bipolar electrodes t the tip was inserted int a tecubital vein Under fluoroscope the tip of the catheter was placed in the apex of the right entricle The heart w paced at a rate of 70 per minut nd the attacks then ceased.

It was noted 32 hours later that 10 t 15 per cent of the impulses from the pacemaker failed t produce ventricular contractions, and t the same time there were *jerk g movements of the whole lest syn kronous with the pacemaker impulses.*

The catheter was left in place while thora cotomy w performed The peric rdial ca ity was found t contain 300 c of blood a ell as the tip and the dist l 10 cm of the catheter hich had perforated the a terior wall of the right entricle A permanent pacemaker impl nted. There was massive bleeding when the catheter a withdrawn but it w easily controlled by sut ring the myocardium. The postoperati course neventful.

This perfor tion of the catheter brought the tip close t the inner thoracic w ll and produced muscular contractions at each electric l stimulation This case also corroborates the view that when perforation by catheter is suspected it should be left in place til any possible bleeding may be controlled

*U S. Catheter Company

at thoracotomy Another ttempt at transvenous pacing, as has been suggested, might be hazardous.

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The lack of influence of end and side orifices in cardiac catheters on venous pressure recording

Because it may be necessary to use cardiac catheters with orifices that are located t different sites near their tips, tudy as undertaken t learn if the pressures in small pulmonary eins that are measured with end-orific catheter differ from those measured ith side-orifice catheter

Fi mongrel dogs were anesthetized with rethane After endotracheal intubation, they were given 100 per cent oxygen mixed with room air at the rat of 2 5 L. per minute. Two yellow KIF catheters (Nos 1 and 2) were introduced transeptally under fluoroscopic control into the left trium and then passed into the same small pulmonary ein. A radiopaqu polyvinyl catheter (I D 0 51 mm O D 0 91 mm) w th an end orifice was passed through the No. 1 KIF and ad anced into the small pulmonary ein Another poly inyl catheter of the same size with side orifice was passed through the No. 2 KIF and positioned in the same

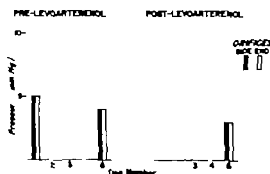


Fig. 1 Comparison of pressures recorded in the same small pulmonary vein with side-orifice and end-orifice catheters. A before levarterenol B after levarterenol

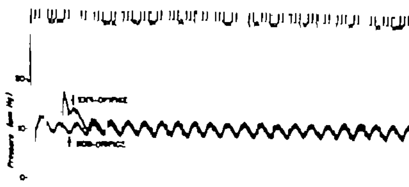


Fig. 2 Small pulmonary vein pressures recorded simultaneously with end-orifice catheters.

small pulmonary vein as the end-orifice catheter such w that the tips of the 2 catheters lay side by side The 2 yellow Kifa catheters were then connected through polyethelene tubings to similarly alibrated Statham strain gauge transducers (P23Db) and pressures were simultaneously recorded on Electronics for Medicine m ltichannel recorder I 3 dogs the pressures were measured before nd after intravenous infusion of levarterenol

Figs. 1 and 2 summarize the result The mean pressure measured in the small pulmonary vein with the 2 catheters were strikingly similar (Fig 1) The 2 catheters lso recorded the same time-courses of hange in pressure (Fig 2). Because of the rates of linear flow and the relatively low magnitudes of pressure in the pulmonary veins it is not surprising that the levels of pressure recorded by the 2 catheters were essentially the same

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Book reviews

LECTURES ON PREVENTIVE CARDIOLOGY By Jeremiah Stamler M D New York 1967 Grune & Stratton Inc 434 pages Price $18.75

This monograph includes series of lectures summarizing the ma y years of detailed and extensive work of Dr Stamler the cause of cardia disease especiall arteriosclerosis. H has been particularly interested the factors which ma be identified that produce or predispose to coronary heart disease Once these are identified prevention becomes more successf l. There are 19 chapters to this book. H presents statistical data concerning the roles of such factors as sex, age smoking diet and hypertension in the production of coronary disease. Those who ha ttended his lectures and scientific addresses will recognize his tables nd charts immediately Chapters on congenital, hypertensiv pulmonary rheumatic and iatrogenic heart diseases are included The book is well written and not on heavy skin paper This is good book by man who has devoted his efforts to the prevention of heart disease It summarizes his work nd ideas extremel ell

CARDIAC ACEMAKERS. B Harold Siddons, M Ch and Edgar Sowton, M D American Lecture Series, Springfield, Ill 1967 Charles C Thomas, Publisher 321 pages. Price $16.27

I few reas of cardiology have the developments been more rapid and dramatic than in the use of electronic equipment for artificial pacing of the heart. I this monograph, the authors ha presented scholarly contribution to this field in highly readable and academic manner I cluded are chapters devoted to an historical review etiology of Stokes-Adams disease, clinical presentation drug treatment short-term pacing long term pacing, linical results, threshold for stimulation, and hemodynamic changes during artificial pacing The material is well documented with pproximately 900 references included. Of additional alue is the presentation of details of approximately 15 pacemakers manufactured in several different cou tries. These include photographs, circuits, nd detailed specifications. The text is particularly aluable since the authors quote from their own significant experience stating personal preferences in regard to choice of pacemakers, techniques of placement nd drug therapy They currently use the endocardial enous electrode method with fixed-rate unit in the majority of patients requiring pacing This monograph is strongly recommended to anyone who is invol ed with the selection nd therapy of patients being considered for cardiac pacemakers. It represents significa t contribution t the cardiology literature

EXPLORACION CARDIOVASCULAR Y FONO MECANOCARDIOGRAF A CLINICA. By Bernardo L. Fishleder and Ignacio Cha ez, Institut Nacional de Cardiologia de Mexico Mexico City 1966 La Prensa Medica Mexicana, 791 pages.

This book, the most comprehensive treatise of ts kind in the Spanish language, should remain a valuable guide to the physical diagnosis of cardiovascular disease It is divided int tw sections the first deals with the physiologic and technical principles related to the detection and graphic recording of heart sounds, precordial movements and arterial and venous pulses the second is devoted to a detailed discussion of the applications of these methods to the clinical study of congenital and acquired heart disease, including hapter on arrhythmias. Extensive but concisely written coverage of these topics is provided in both sections The chapters on congenital heart disease are particularly outstanding The bibliography which contains references p to 1964 is exhaustive and the illustrations are of excellent technical quality Highly recommended.

Books reviewed

ANGIOLOGIE FIBEL. By Werner Schoop. Stuttgart, 1967, Georg Thieme Verlag. 154 pages.

GOUT. Ed. 3. By John H. Talbott and J. E. Seegmiller. New York, 1967, Grune & Stratton, Inc. 296 pages. Price $12.50.

LA ROTTURA DEL CUORE. Collana di monografie cardiologiche No. 19. B. C. Fauda, V. Gregolata, and G. Sfondrin. Milano, 1967, Editore Recordati, Industria Chimica de Farmaceutica. 123 pages.

THE NATURE OF LIFE AND CANCER. By Benedict V. Fata and Frank J. Perone. New York, 1967, Philosophical Library. 98 pages. Price $1.75.

MANUAL OF PREOPERATIVE AND POSTOPERATIVE CARE. By Henry T. Randal, James D. Hardy, and Francis D. Moore. Philadelphia, 1967, W. B. Saunders Company. 506 pages. Price $8.50.

BEDSIDE MEDICINE. ed. 2. By I. Snapper and Alvin I. Kahn. New York, 1967, Grune & Stratton, Inc. 824 pages.

Editorial

Coronary arteriography

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The technique of coronary arteriography has developed over the past decade to the point where it can now be widely applied with relative safety to the clinical evaluation of selected patients. Several recent reports have described clinical experience with the technique and have correlated clinical data with arteriographic findings. It is apparent that coronary arteriography will be applied increasingly to the problems of patients in future years. It is therefore appropriate to evaluate the present status of the technique with particular regard to 4 basic questions: (1) What is the risk of the procedure? (2) What are the clinical indications for its use? (3) What ancillary clinical studies can supplement arteriographic data? (4) What critical information can be obtained from the procedure?

It is evident that coronary arteriography carries a definite risk to life as well as a risk of transient and possibly permanent vascular damage. Any intra-arterial injection of a contrast agent involves a calculated risk, but this need not contraindicate a necessary procedure in properly selected patients. The magnitude of the risk must be assessed. Information from several centers indicates that coronary arteriography in experienced hands involves a potential mortality rate of 0.3 per cent.[1-3] The risk is largely confined to patients with severe coronary disease. Transient episodes of cardiac arrhythmias, hemorrhage, or vascular thromboses occur in approximately 1 to 7 per cent of patients, depending on the technique employed and the experience of the group.[1,2,4,5] Again, such complications are more common in patients with coronary artery disease and peripheral arteriosclerosis. The incidence of permanent vascular injury such as arterial thrombosis with intermittent claudication is lower.

Experienced personnel, careful monitoring of cardiac rhythm, and adequate facilities for immediate resuscitation which include cardioversion and prompt surgical intervention in the event of vascular occlusion or hemorrhage are mandatory to achieve a low incidence of complications. Under ideal conditions, the risk should be no greater than that of thoracic aortog-

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raphy or other intracardiovascular diagnostic procedures. The critical element therefore is the degree to which the clinical indications and the information provided justify even the relatively small risk involved.

Indications. The 6 general indications for coronary arteriography are summarized below in order of their relative importance.

1. INCAPACITATING ANGINA PECTORIS OR SEVERE CORONARY DISEASE WHICH REQUIRE CONSIDERATION OF SURGICAL INTERVENTION. Without a preoperative anatomic map of the extent and distribution of the coronary disease, the potential usefulness of surgery cannot be determined. Furthermore, without angiography, neither the type of surgery nor the site of profitable surgical attack can be rationally defined.

2. VALVULAR HEART DISEASE WHERE CORRECTIVE SURGERY IS POSSIBLE BUT WHERE EVIDENCE OF ASSOCIATED CORONARY DISEASE IS PRESENT. In most instances, hemodynamic assessment alone is sufficient since if a valvular lesion is functionally severe enough to require surgery, improvement will result even in the presence of coronary disease. In some patients valvular disease of moderate severity may be associated with severe coronary disease. Under such circumstances, valve surgery may not be helpful and the operative risk may be high. Coronary arteriography will demonstrate the presence and amount of associated coronary disease and may reveal lesions of the coronary arteries that are suitable for endarterectomy.

3. CLINICAL SYMPTOMS OR SIGNS SUGGESTIVE BUT NOT DIAGNOSTIC OF CORONARY DISEASE IN THE RELATIVELY YOUNG PATIENT. Usually there is chest pain suggestive of angina or myocardial ischemia or abnormalities are present in the electrocardiogram which suggest myocardial infarction. In such patients it is important to determine if the risk of the procedure is less than the risk of remaining ignorant about the state of the coronary circulation. There is a definite risk in *not* doing an arteriogram in such circumstances, particularly if long term anticoagulant administration is contemplated. The risk of cardiac neurosis, despondency, and fear of death in a patient with a normal coronary circulation are also definite. The most valuable contribution of coronary arteriography in such a setting is the demonstration of a normal coronary vascular bed. The decision to perform an arteriogram in this group of patients can be made only on an individual basis.

4. EVALUATION OF THE EFFECTIVENESS OF CORONARY SURGERY. At a moment when the enthusiasm for coronary surgery seems heightened, it is essential to assess the degree to which such procedures as endarterectomy or myocardial revascularization have improved the delivery of blood to the myocardium. Although the coronary arteriogram affords a relatively gross anatomic view, it can, nevertheless, indicate that stenosis has been relieved or that an internal mammary implant provides a route of perfusion of major myocardial vessels.

5. ANGINA PECTORIS IN THE RELATIVELY YOUNG PATIENT. While symptoms may not be serious enough to warrant surgery, coronary arteriography will allow confirmation of the diagnosis, demonstrate the presence of operable lesions, and occasionally reveal unusual lesions of the coronary circulation such as an aberrant coronary artery arising from the pulmonary artery. This is a relative indication which must be evaluated on an individual basis.

6. HEART FAILURE OF UNKNOWN ORIGIN. Although the diagnosis of cardiomyopathy can usually be made on the basis of clinical evidence alone, ischemic heart disease may occasionally present with a similar clinical picture. A normal arteriogram will exclude the latter diagnosis and allow more intelligent medical management, but the information rarely influences the ultimate outcome of the illness. The decision to perform an arteriogram under these circumstances can be made only on an individual basis.

Coronary arteriography is contraindicated in the presence of acute myocardial infarction unless direct surgical intervention is deliberately planned under this circumstance.

Value of ancillary studies. Complete clinical and pertinent laboratory studies which include an electrocardiogram should precede coronary arteriography. The ECG exercise test has been shown to be an essential preliminary test. Most workers

gree that sufficient exercise should be performed to produce limiting symptoms or a heart rate in excess of 150 beats per minute. This usually requires graded treadmill exercise with continuous monitoring of the ECG. A clearly positive test in the absence of valvular or myocardial disease or digitalis is usually associated with severe coronary disease and may obviate the need for arteriography unless surgery is contemplated. A negative test does not exclude the presence of coronary disease. Other methods of evaluation such as family history, serum lipids, blood pressure, body weight, personality profile, or the ballistocardiogram supply little additional critical data. Such information is more useful in screening population groups than identifying the presence of coronary disease in the individual patient. The presence of an infarct pattern in the ECG is usually associated with significant obstructive coronary disease that involves at least 1 major vessel; many electrocardiographic abnormalities have been found in patients with normal arteriograms.

Information provided. A normal coronary arteriogram excludes obstructive disease of the major coronary vessels as the cause of clinical symptoms or abnormalities in the ECG. It cannot detect disease of small coronary vessels, but this is a rare condition.

Abnormal arteriograms must be interpreted with the aid of clinical data and the results of the ECG exercise test. Clinical symptoms are usually associated with occlusive disease involving at least 2 major coronary arteries, but symptomatology cannot be predicted from the appearance of the arteriogram above. A clear history of angina pectoris or a positive ECG exercise test will confirm the functional severity of the lesions seen, but a negative ECG exercise test will not exclude symptomatic disease. Moderate abnormalities in the arteriogram such as occlusive disease that involves only 1 coronary artery or nonocclusive narrowing of 2 branches are usually not associated with clinical symptoms. The evaluation of such findings is difficult.

In the arteriographic evaluation of patients for coronary artery surgery, the most favorable operable lesion is a severe degree of short stenosis of a major coronary artery located close to the aortic orifice. The obstruction can be removed by incision of the artery or by endarterectomy from the aortic ostium. It is essential that patency of the distal vessel be demonstrated. This can usually be detected in serial films by delayed filling via collaterals. The incidence of such lesions is unfortunately low; it occurs in about 2 to 4 per cent of patients with classical angina.[8] The incidence may be greater in patients with variant forms of angina, but this has not been clearly established.

Revascularization of the myocardium by an internal mammary artery implant may be performed if the arteriogram demonstrates occlusive disease confined to the left anterior descending coronary artery and especially if some collateral flow is already present as evidenced by a "myocardial blush" or late opacification of distal vessels by collateral flow in serial films. Total absence of vessels or lack of evidence of collateral flow together with QRS abnormalities in the ECG suggests the presence of myocardial scarring which would make a revascularization operation unwise.

The arteriogram may also be useful as a guide to the method of medical management used in patients with angina pectoris. Patients who have "walk through" or "second wind" angina and who have good collateral vessels or *local stenotic lesions* without occlusion demonstrated by angiography may be improved by a program of daily graded exercise.

While coronary arteriography provides much information for the clinician and surgeon, it is clear that anatomical data alone will not predict the degree of functional disturbance that may be present. No consistent pattern of coronary abnormality has been associated with distinctive clinical syndromes. There is a great need for a system of *classifying* abnormal coronary arteriograms that would be more closely related to the degree of functional impairment of coronary flow.

It is apparent that future technical improvements will permit wider application of coronary arteriography. Improved methods of surgical treatment, medical management, and prophylaxis will increase the

need for the procedure. Coronary arteriography cannot be casually performed. Divorced from trained personnel and adequate equipment its information yield will be low, its hazards will increase, and its role in the framework of medical diagnosis will fall rapidly into disrepute. As in the application of all diagnostic methods the balance between risk and yield must be kept clearly in focus and the indications for this unique procedure must be carefully observed.

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Clinical communications

Electrocardiographic patterns at the termination of atrial flutter

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One approach toward a better understanding of the contiguous electrocardiographic waves of atrial flutter might be in observations at its onset or ending. Unfortunately as noted earlier most if not all of the reported onsets deal with impure flutter i e fibrillation However the termination of pure classical atrial flutter has been recorded several times. The purpose of this study is to add new examples and to review such instances, which appear to take three forms (a) in the dying heart (b) at transition to atrial fibrillation and (c) at restoration of sinus rhythm

The dying heart

Fig 1 presents events in a man dying with a massive, acute pulmonary embolism Nodal rhythm and a reciprocal cycle were followed by atrial flutter with which the atrial rate slowed progressively from 192 to 130 per minute Intraventricular block preceded ventricular standstill Cessation of ventricular activity was followed for a while by atrial waves of low amplitude Use of a cylinder lens[2] yielded somewhat more detail in such waves, but even with such magnification (Fig 2) they were directed only upward

Transition to atrial fibrillation

Figs. 3 and 4 show the spontaneous transition of flutter to fibrillation after preliminary acceleration of the atrial rate of the former In one of these patients records also show the reverse transition both spontaneously (Fig 4) and during massage of the carotid sinus (Fig 5)

Figs 6 and 7 present the transition of atrial flutter to fibrillation in another patient during carotid sinus stimulation In this case the base line appears to be isoelectric for 0 08 second at the end of flutter

Restoration of sinus rhythm

Perhaps of greatest interest are the records of Fig 8 in which sinus rhythm spontaneously replaced atrial flutter no previous attention seems to have been given to such a change nor any other examples discovered. From 3 patients, the records appear to be nearly identical flutter ceases shortly (about 0 04 second) after the wave s nadir and subsequently there is a rather long pause prior to resumption of sinus rhythm In Fig 8,*A* the final inverted flutter wave coincides with an exaggerated inversion of T in Fig 8 *C* the baseline wanders a bit after the final inverted flutter wave but is not identical to the gentle downsweep of the other flutter cycles

Discussion

The dying heart A termination of atrial flutter somewhat comparable to th t of

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Fig. 1. Sequential but not consecutive strips of Lead II showing atrial flutter at death of a man with massive pulmonary embolism. (Record obtained by Robert Rou tree M.D. April 11 1950.)

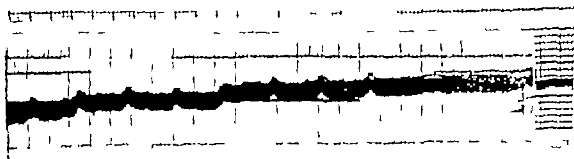


Fig. Terminal trip of Fig. 1 mag ified by mea of cylindr lens.



Fig 3 Spontaneous transition of trial flutter to fibrillation show in second of tw consecutiv strips of Lead V M n, 49 years old with mitral stenosis nd insufficiency receiving digitalis nd quinidine Aug 18 1953



Fig 4 A spontaneous transition of trial flutter t fibrillation Lead V *B* spontaneous transition of atrial fibrillation to flutter Lead II Hypertensiv woma 56 ears ld, with hypokalemia and receiving digitalis, Aug 12 1964



Fig 5 Transition of atrial fibrillation to flutter and the reverse during and immediat ly after carotid sinu massage T consecutiv strips of Lead II same patient nd dat as in Fig 4

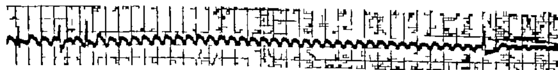


Fig 6 Transition of atrial flutter t fibrillation during carotid inu massage Lead II Man, 50 years ld with angina pectoris, with paroxysmal trial flutter 6 months after otomy for aortic tenosis receiving digitalis J l 18, 1955

A

B

C

D

Fig 7 Enlargement of portions of Fig 6. 1 trial flutter before nd t onset of 6 second entric lar t le B termination of entric lar sy t le Note brief isoelectric line just before entricular esc pe f brillat on subsequent t latter C nd D segment of second trip w th cylinder lens for ert al nd horizontal mag fi- t on respectiv l isoelec ric phase persists despit use of the lens.

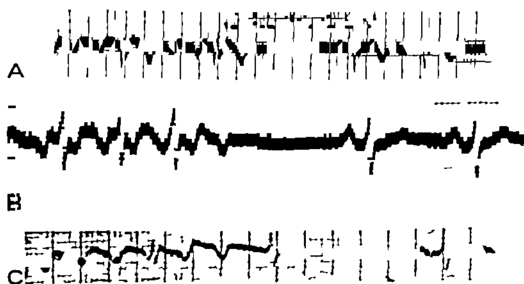


Fig 4 Spontaneou terminat on of t ial flut er w th resumpt on of si rhythm fter brief pa se In 3 pa tient (Lead III (From Kat L N nd Pick A Clinical lectrocardi gr phy I rt I The rrhythmia Philadelphia 1956 Le & F biger 1 243) B Le III prev ou l unreported C Le I III (F om Whit P D nd Griffith C C J A M A 169 5?6 1959)

Fig 1 was reported by Enselberg Interest centers about th fact that the final atrial complexes were directed only upward in Lead II in the direction once alleged to represent repolarization in atrial flutter

Transition to at ial fibrillation This rarely recorded change ha been reported both during carotid sinus stimulation[1] and spontaneously[4] it further had been noted by others in both circumstances, but records were not presented[1,4] The nterest and importance of this transition

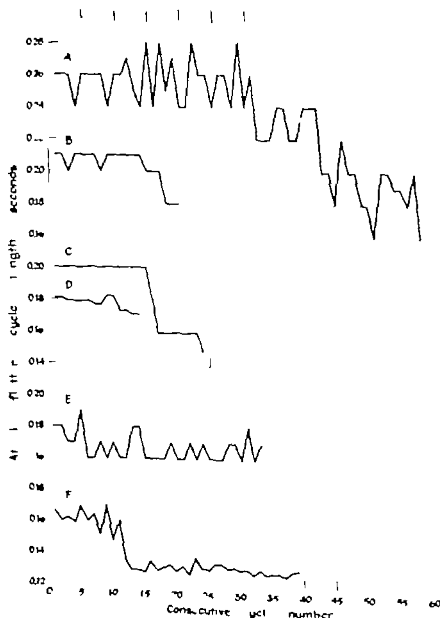


Fig 9 Dura ion of trial flutter cy le in consecuti cy les prior to transition to fibrillation (*A* *E*). Spontaneous hanges in 1 and *B* (data from Figs. 3 and 4 respectively), otherwise during indirec agal stimulation. *C* is after Bruna Reid, and Scherf[3] *D* is calculated after M Millan and Bellet *E* is from Fig 6. *F* is after Wilson,[a] ithout transition t fibrillation. Note relatively abrupt acceleration of rate in 1 *B* *C* and *F* with but little hange in *D* and *E*. Of the 3 patients ith transition to atrial fibrillation and ith long entricular cycles, the transition followed immediately upon entricular activation in all (*A* *C* and *E*) and en ricular escape of these (*E*)

appear to be in this light it may throw m the initiation f atrial fibrillation particularly via vagal mechanisms [17]

Ordinarily stimulation of the vagus by massage of the carotid sinus in man during flutter increases the degree of arteriovenous block but has little or no effect on atrial rate despite ventricular slowing or stand still With nonvagal ventricular asystole the atrial rate either declines [7] or remains constant However certain early studies in dog and man[19] reported atrial acceleration in flutter upon vagal stimulation and this has been stressed subsequently Review of the present illustrations and other relevant ones suggests that acceleration is more likely to occur abruptly than gradually fibrillation may supervene when the atrial cycle length falls t 0 18 0 16 or 0 15 second in different patients or may persist despite a decline from 0 16 to 0 13 second (Fig 9)

Review of the illustrations furthermore reveals another phenomenon which seems to have escaped comment and which may prove to be more important than atrial acceleration In the present Figs. 3 6 and 7 and also in three published tracings the transition of atrial flutter to fibrillation appears to follow immediately a ventricular complex (sometimes ventricular escape as in Figs. 6 and 7) this was not seen in one other published human record and the ventricular rate was too rapid for any such judgment in Fig 4 and elsewhere In sum five of six recorded transitions in man suggest an intervention f retrograde conduction to the atria in the initiation f fibrillation In canine flutter this may have occurred once but not in another report [22]

In each of three records of the initiation of atrial fibrillation from sinus rhythm in man retrograde conduction may have occurred at least one of these involving ventricular escape [22,23] In the similar transition in dogs, three papers call attention to this phenomenon [24] and illustration in several other publications reveal it [28,29] Only a few show the onset of fibrillation unrelated to a ventricular cycle [27,28,29,30]

The reverse transition of atrial fibrillation to flutter (Fig 5) during carotid sinus stimulation may have occurred by chance or in spite of the latter rather than because of it for it occurred spontaneously as well (Fig 6) There seem to be no other published examples of this in man although something of the sort was found once by Lewis[31] in the dog

Restoration of sinus rhythm Atrial flutter sometimes is replaced by sinus rhythm during vagal stimulation with or without preliminary acceleration in both man[32,33] and dog

Of great interest are the three spontaneous transitions shown in Fig 8 without preliminary changes in the flutter cycle length Two records in dogs also show abrupt termination of flutter to sinus rhythm [33,34] Of Fig 8 two tracings had been published by other authors[35,36] while one is original All were recorded in limb Lead II or III Each shows restoration of the isoelectric line shortly after the wave s nadir Fig 6 may represent another instance. Thus, there is little or no upward wave which once was thought to represent repolarization in flutter still another bit of evidence against the validity of that concept. Next it may be seen that the isoelectric line is nearly centered in relation to the flutter wave this important fact enables one to place the null point centrally in vectorcardiographic analyses of flutter at least in the most valuable longitudinal axis. Beyond this one may only speculate upon the identical appearances of the three records. Coincidence is of course possible but seems unlikely Vectorial analysis would indicate that in each of these 3 (or perhaps 4) patients flutter ended just before the momentary atrial vector should have commenced a downward rightward and forward direction subsequent to its opposite progression. If the specialized internodal fibers of the atria are indeed involved as the central path for an essential portion of an entrapped circuit wave in flutter then these findings speculatively suggest termination in or near the sinus node

Summary

Electrocardiograms are presented which show the termination of pure classical atrial flutter (a) in the dying heart (b) in transition to atrial fibrillation and (c) at the spontaneous restoration of sinus

rhythm These unusual records are discussed in relation to relevant records published by others and also to certain theoretical implications particularly concerning (a) background data required for vectorial analysis of atrial flutter and (b) the apparent involvement of retrograde conduction perhaps via a vagal mechanism at times at the transition to fibrillation

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Simplified clinically applicable vectorcardiographic diagnosis of left ventricular hypertrophy (Frank lead system)

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It is the purpose of this report to present the data from vectorcardiograms (VCG) taken in the course of a study on patients with established left ventricular hypertrophy (LVH) Pertinent medical literature is reviewed and summarized. An attempt is made to demonstrate a simple clinically applicable means of identifying the presence or absence of LVH using the VCG In this study the VCG analysis is based primarily upon a study of the magnitude of the maximum QRS vector in the frontal horizontal and left sagittal planes nd on the angular displacement of the maximum QRS vector in the horizontal and left sagittal planes The results indicate that there is a wide spectrum of VCGs observed in patients with proven LVH nd that LVH can be diagnosed simply and quickly using the VCG

Methods and patients studied

The technique of VCG registration was that devised by Frank. Placement of the electrodes was at the level of the fifth intercostal space at the sternal border All patients were in the fasting state and were in the supine position The tracings were taken during normal resting respiration. The recording equipment consisted of a Sanborn 350 Polygraph Recorder (eight-channel) A Leica M 3 camera with a Visoflex attachment and a 90 mm. lens using 35 mm Panatomic X film photographed the calibrations and the frontal horizontal and left sagittal VCG loop projections from the oscilloscopic screen The films were printed on Kodabromide A 3 lightweight paper Interruptions in the VCG loops occurred 400 times per second each dot thus representing 2.5 msec The tear-drop-shaped dashes point in the direction of rotation Standard calibrations were such that 1 0 millivolt (mv) caused a deflection of the dot on the oscilloscopic screen of 10 cm. in both the horizontal axis and the vertical axis Fig 1 demonstrates the conventional eference frames for the horizontal frontal and left sagittal planes. The left sagittal plane was used throughout the study as recommended by the Committee on Vectorcardiography

In addition to the VCG other tests recorded on each patient the same day were a standard twelve-lead electrocardiogram recorded by either a Sanborn Viso-100 direct writing instrument or a Cambridge Simpli-Scribe direct writing instrument complete blood count, urinalysis, cardiac series x-rays which included posteroanterior lateral right anterior oblique

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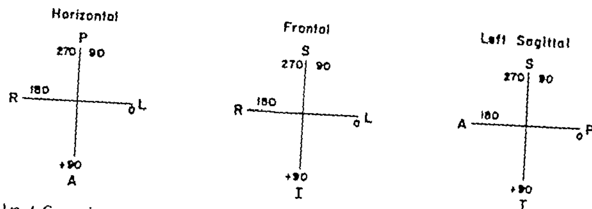


Fig. 1. Conventional reference frames for the horizontal, frontal, and left sagittal planes; the numbers refer to degrees. R, right; L, left; A, anterior; P, posterior; I, inferior; S, superior.

and left anterior oblique chest x rays with barium swallow. Each patient was examined on the same day as the tests were performed.

LVH was considered present on physical examination if the left ventricular thrust on the anterior chest of the patient was exaggerated in amplitude and more sustained in time than normal as detected by the palpating hand. Frequently the left ventricular impulse was displaced to the left and inferiorly. LVH was considered present on radiologic examination if the posteroanterior chest x ray disclosed an increased convexity and a displacement to the left of the lower left border of the heart and if the left anterior oblique chest x ray disclosed overlapping of the dorsal spine by the posterior aspect of the left ventricle.[25] LVH was considered present on the electrocardiogram according to the criteria of Sokolow and Lyon.

VCG analysis included the following: (1) horizontal plane loop configuration and direction of inscription, (2) magnitude (mv.) of the maximum QRS vector in horizontal, frontal, and sagittal planes: the maximum QRS vector was taken as the longest diameter of a loop drawn from the point of origin, and (3) displacement of the angle of the maximum QRS vector in the horizontal and left sagittal planes. P and T loop vectors were not analyzed in this study. With practice it was possible to complete the analysis of each VCG without hurrying in less than 2 minutes.

Twenty patients with LVH comprised the study group (Table I). Nineteen were men and one was a woman. Ages ranged from 30 years to 66 years with a mean age of 43 years. The diagnosis of LVH was established by the physical examination, cardiac series x rays, and the twelve-lead electrocardiogram according to criteria mentioned already.[24,26] Excluded from the study was any patient with LVH who had additionally (1) a history of angina pectoris or myocardial infarction, (2) an electrocardiogram consistent with myocardial infarction, (3) an electrocardiogram whose QRS duration was greater than 0.11 seconds, or (4) a history or signs of right ventricular failure. The etiology of the LVH varied. Thirteen patients (65 per cent) had rheumatic heart disease, 4 patients (20 per cent) had hypertensive cardiovascular disease, 2 patients (10 per cent) had traumatic heart disease, and one patient (5 per cent) had recurrent paroxysmal atrial tachycardia. Thirteen (65 per cent) had predominant aortic valve lesions: in 12 of these the etiology was rheumatic heart disease and in one the etiology was trauma. 9 were predominantly aortic regurgitation and 4 were predominantly aortic stenosis. One patient with rheumatic heart disease had mitral regurgitation and one patient had a ventricular septal defect secondary to trauma.

Twenty patients without LVH comprise the control group (Table II). All were men. Ages ranged from 28 years to 56 years with a mean age of 39 years. The diagnosis of LVH was excluded by physical examination, cardiac series x rays, and a twelve-lead electrocardiogram according to criteria mentioned already.[24,26] Eleven patients (55 per cent) had no cardiovascu

Table I Clinical data on patients with LVH

Case No	*Age (yr)*	*Etiology**	*Predominant lesion*†	*Physical examination*‡	*X-ray*‡	*ECG*‡	*Horizontal loop configuration*
1	50	RHD	MR	+	+	+	IB
2	35	RHD	AR	+	−	+	IA
3	47	RHD	AR	+	+	+	IB
4	49	RHD	AR	−	+	+	II
5	47	HCVD	—	−	+	+	IB
6	37	RHD	AS	+	+	+	IA
7	43	Trauma	AR	+	+	+	IA
8	38	HCVD	—	+	+	+	II
9	45	RHD	AR	+	+	+	IA
10	46	RHD	AS	+	−	−	IA
11	45	RHD	AS	+	+	+	IB
12	38	RHD	AR	+	+	+	II
13	38	RHD	AR	+	−	−	IA
14	43	HCVD	—	+	+	+	IA
15	35	RHD	AS	+	−	+	IA
16	41	RHD	AR	+	+	−	II
17	66	HCVD	—	+	+	−	IB
18	30	RHD	AR	+	+	+	IA
19	53‡	PAT	—	+	+	−	IA
20	43	Trauma	VSD	+	−	+	IA

*RHD rheumatic heart disease HCVD hypertensive cardiovascular disease PAT paroxysmal atrial tachycardia.
†MR mitral valve regurgitation AR aortic valve regurgitation AS aortic valve stenosis, VSD ventricular septal defect.
‡Presence (+) or absence (− of hypertrophy by this technique according to criteria outlined in the text
§Only woman in series

Table II Summary of data on 20 control patients (without LVH)*

	Age (yr)	*QRS vector*			*QRS angle*	
		H	*F*	*S*	*H*	*S*
Mean	39	1 37	1 39	1 23	−41	+28
Range	28 to 56	0 96 to 1 76	0 91 to 2 35	0 85 to 1 80	117 to +25	−8 to +75

*Ten had horizontal loop Type IA 6 had Type IB 4 had Type II none had Type III QRS vector refers to the magnitude in millivolts of the maximum QRS vector QRS angle refers to the displacement in degrees of the angle of the maximum QRS vector H horizontal plane; F frontal plane S left sagittal plane.

lar disease 6 patients (30 per cent) had rheumatic heart disease with valvular lesions that were hemodynamically insignificant 2 patients (10 per cent) had had systemic arterial hypertension but received treatment for their hypertension and had normal blood pressure recordings during the period of this study one patient (5 per cent) had a history of paroxysmal atrial tacycardia.

Results

Horizontal plane loop configuration and direction of inscription Three types of horizontal loop configuration occur (Fig 2) and the classification is the same as that reported in an earlier study Sixteen cases (80 per cent) were inscribed in a counter clockwise direction (Type I) In 11 cases (55 per cent) the initial inscription of the loop was to the right and anteriorly (Type

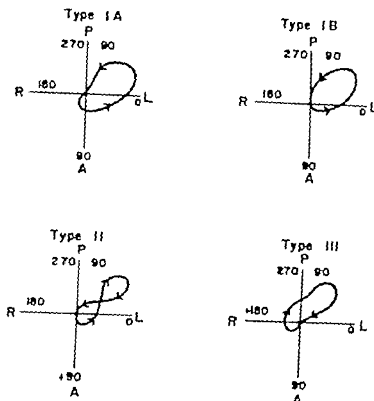


Fig. 2. Types of horizontal loop configuration. The numbers refer to degrees. R, right; L, left; A, anterior; P, posterior. The arrows in the drawn loops indicate the direction of inscription.

IA) and in 5 cases (25 per cent) the initial inscription of the loop was to the left and anteriorly (Type IB). In 4 cases (20 per cent) the loop gave a figure-of-eight configuration (Type II). No case of Type III configuration was present in this study (i.e., clockwise inscription of the loop with the initial inscription to the right and anteriorly).

Magnitude of the maximum QRS vector in the horizontal, frontal, and sagittal planes. Table III contains the VCG data of the LVH patients and is arranged according to the horizontal loop pattern. The mean magnitude of the maximum QRS vector in the horizontal plane for all cases was 1.82 mv. and ranged between 1.00 and 2.52 mv. The mean magnitude for Type IA was 1.80 mv., for Type IB was 1.81 mv., and for Type II was 1.91 mv. In 60 per cent of all cases the magnitude was equal to or greater than 1.50 mv.

The mean magnitude of the maximum QRS vector in the frontal planes for all cases was 1.68 mv. and ranged between 0.97 and 2.51 mv. The mean magnitude for Type IA was 1.71 mv., for Type IB was 1.53 mv., and for Type II was 1.76 mv. In 75 per cent of all cases, the magnitude was equal to or greater than 1.25 mv.

The mean magnitude of the maximum QRS vector in the sagittal plane for all cases was 1.49 mv. and ranged between 0.69 and 2.87 mv. The mean magnitude for Type IA was 1.49 mv., for Type IB was 1.46 mv., and for Type II was 1.51 mv. In 70 per cent of all cases the magnitude was equal to or greater than 1.20 mv.

The displacement of the angle of the maximum QRS vector in the horizontal and left sagittal planes. The mean displacement of the angle of the maximum QRS vector in the horizontal plane for all cases was −38 degrees and ranged between +8 degrees and −100 degrees. In the horizontal plane of loop pattern Type IA the mean angle of the maximum QRS vector was −33 degrees, for Type IB the mean angle was −45 degrees, and for Type II the mean angle was −43 degrees. In 50 per cent of all cases the maximum QRS vector was directed −18 degrees or more posteriorly

Table III. VCG data on 20 patients with LVH

Loop type	No. of patients	QRS vector H	QRS vector F	QRS vector S	QRS angle H	QRS angle S
IA	11	1.80 (1.00 to 2.59)	1.71 (0.97 to 2.48)	1.49 (0.69 to 2.87)	−33 (−10 to −80)	+31 (−11 to +79)
IB	5	1.81 (1.10 to [illegible])	1.53 (1.00 to 2.51)	1.46 (0.98 to 3.03)	−45 (+8 to −100)	+19 (−10 to +55)
II	4	1.91 (1.47 to 2.32)	1.76 (1.25 to 2.48)	1.51 (1.17 to 2.05)	−43 (−15 to −78)	+28 (+14 to +50)

*QRS vector refers to the magnitude in millivolts of the maximum QRS vector. QRS angle refers to the displacement in degrees of the angle of the maximum QRS vector. H, horizontal plane; F, frontal plane; S, left sagittal plane. Figures in parentheses refer to ranges encountered.

Mean displacement of the angle of the maximum QRS vector in the left sagittal plane for all cases was +27 degrees and ranged between −11 degrees and +79 degrees. In the left sagittal plane of loop pattern Type IA, the mean angle of the maximum QRS vector was +31 degrees; for Type IB, the mean angle was +19 degrees; and for Type II, the mean angle was +28 degrees. In 80 per cent of all cases, the maximum QRS vector was directed +50 degrees or less in the left sagittal plane.

Discussion

It is acknowledged generally that the Frank system for recording VCGs is a simple, accurate, and clinically practical system that provides three truly orthogonal leads for presentation on an oscilloscope. Earlier studies using the Frank system outlined the VCG findings in normal subjects[4] and in patients with LVH. Unfortunately, these earlier studies were not performed in the same way, employing different techniques and methods of selection of patients (Table IV); thus, valid comparison of the results of these studies is not possible. Such marked variations are bound to result in different findings, and indeed, when one seeks to compare one study with another, one is bewildered by the wide range of normal and abnormal values. The present study used ambulatory patients in an outpatient Veterans Administration clinic. These patients reported to the clinic at 4 to 6 month intervals from all parts of Georgia. For the most part they were employed gainfully and reported to the clinic not because they felt sick, but because of a previously and regularly scheduled appointment. Many previous studies were on hospitalized patients or on autopsy cases and represent probably patients with a more severe circulatory problem than those included in the present study. Patients in the present study have for the most part a mild or early form of LVH. This would account probably for the lower magnitude of QRS vectors found in these cases as contrasted with earlier studies.

Other variables noted in earlier studies in which the Frank VCG system was used include (1) racial differences, (2) the taking of tracings with subjects or patients in the sitting position, (3) the study of tracings whose QRS intervals were as great as 0.12 second, (4) the placement of electrodes at the fourth intercostal space at variable reference points from the midline, (5) the age of patients studied, (6) different male-female sex ratio, and (7) differences in the cardiovascular lesion causing LVH. It is not known how much change in the VCG these variables induce, but it is logical to assume that they cause some change and thus introduce a technical

Table IX. Summary of data from VCG studies of LVH (Frank lead system)

	QRS vector			QRS angle		Description of patients and/or technique
	H	F	S	H	S	
Groups with LVH						
Present study	1.82	1.68	1.49	−38	+27	Ambulatory clinic patients, few asymptomatic; 19 men and 1 woman; mean age was 43 years; electrodes at fifth intercostal space
Murata and associates	1.50	1.55	1.23	X	X	Japanese autopsy cases; all patients over age 60 years; electrodes at fifth intercostal space
Wallace, McCall, and Estes[23]	2.43	2.15	1.54	−29	+35	All males; all had LVH due to systolic overload; mean age was 51 years; 10 had CHF; electrodes at fifth intercostal space
Bristow, Porter, and Griswold[22]	3.29	2.95	2.31	−32	+22	LVH due to systolic overload; only 2 patients had diastolic overload; mean age was 40 years; electrodes at fifth intercostal space; patients sitting
Varriale, Alfenito, and Kennedy	2.56	2.26	1.89	−40	+20	Thirty-seven men, 13 women; mean age was 53 years; electrodes at fourth intercostal space
Hugenholtz and associates	3.40	X	X	−44	X	Autopsy cases; 17 patients; electrodes at fifth intercostal space; patient sitting
Group without LVH						
Present study	1.37	1.39	1.23	−41	+28	Outpatient clinic patients; mean age, 39 years; 11 men; electrodes at fifth intercostal space
Murata and associates	1.12	1.23	0.89	X	X	Japanese autopsy cases; all patients over 60 years; electrodes at fifth intercostal space
McCall, Wallace, and Estes	1.03	1.25	0.81	+1	+84	Fifty men, 50 women; hospital and university personnel; electrodes at fifth intercostal space; subject supine
Bristow	1.58	1.67	1.24	−33	+39	Seventy men, 4 women; medical faculty and house officers; hospitalized patients; electrodes at fifth intercostal space; subjects sitting
Draper and associates[19]	1.39	1.57	1.32	−33	+48	Hospitalized patients; electrodes at fourth intercostal space
Hugenholtz and Liebman	1.35	1.49	1.19	−18	+72	Hospitalized children; ages from 7 months to 16 years; electrodes at fourth intercostal space
Forkner, Hugenholtz, and Levine[4]	X	X	X	−14	+65	Thirty-six females, 35 men; age range 18 to 36 years; electrodes at fifth intercostal space

*QRS vector refers to the magnitude in millivolts of the maximum QRS vector. QRS angle refers to the displacement in degrees of the angle of the maximum QRS vector. H, horizontal plane; F, frontal plane; S, left sagittal plane; CHF, congestive heart failure; X, data not given.

difference between the results of various VCG studies. Some of the problems of VCG standardization have been noted earlier.[23,1] This discussion emphasizes the need for further standardization of VCG technique.

Earlier studies have demonstrated that three patterns of loops occur in the horizontal plane (Fig.). Type I horizontal loop patterns occurred in 80 per cent of cases in the present study and in 74, 80, 58, and 95 per cent of the series of Varriale, Alfenito, and Kennedy, Bristow, Porter, and Griswold,[22] Wallace, McCall, and Estes,[23] and Murata and associates, respectively. Type II horizontal loop pat-

terns occurred in 20 per cent of cases in the present study and in 18, 17, 38, and 5 per cent of the series of Varriale, Alfenito, and Kennedy, Bristow, Porter and Griswold,[13] Wallace, McCall and Estes,[14] and Murata and associates, respectively. Type III horizontal loop patterns did not occur in this series nor in that of Murata and associates. It occurred in 8, 2, and 4 per cent, respectively, of the series of Varriale, Alfenito and Kennedy, Bristow, Porter and Griswold,[13] and Wallace, McCall and Estes,[14] respectively.

As stated above, the present series of patients cannot be compared in an exact way with earlier studies because of differences in the techniques of the various studies. Thus, the present LVH group displays only a modest shift from normal in the magnitude of the QRS vector and in the displacement of the QRS vector. On the basis of this study, the following criteria for the diagnosis of LVH are proposed: (1) the magnitude of the maximum QRS vector in the horizontal plane must be 1.50 mv. or more; 80 per cent of all of the cases of this study satisfied this criteria; (2) the magnitude of the maximum QRS vector in the frontal plane must be 1.25 mv. or more; 75 per cent of all of the cases of this study satisfied this criteria; (3) the magnitude of the maximum QRS vector in the sagittal plane must be 1.30 mv. or more; 70 per cent of all of the cases satisfied this criteria; (4) the displacement of the angle of the maximum QRS vector in the horizontal plane must be −18 degrees or more posteriorly; 80 per cent of all of the cases of this study satisfied this criteria; (5) the displacement of angle of the maximum QRS vector in the left sagittal plane must be +50 degrees or more superiorly; 80 per cent of all of the cases of this study satisfied this criteria.

Since most of these patients represent cases of early or mild LVH, the suggested VCG criteria for the diagnosis of LVH are the most sensitive of those reported previously. Unfortunately, such sensitive criteria will of necessity lose much of their specificity. Thus there may be some normal subjects, particularly in the younger age group, whose VCG findings will fall within the range of the LVH criteria. In the evaluation of an individual patient, such overlap of normal and LVH criteria must be considered. The merit for this data lies in the demonstration that a patient with early, yet definite, LVH is likely to have a VCG with QRS voltage and angular displacement only moderately different than a normal subject. It is well to remember, however, that it is not necessary for a patient to have great abnormalities in the VCG in order to establish the diagnosis of LVH.

The present proposed analysis of the VCG is based on the method described by Varriale, Alfenito and Kennedy. The criteria suggested in the present study are the most sensitive of any reported to date. If four or five of the criteria are fulfilled, the diagnosis is definite; if three are fulfilled, the diagnosis is probable; if two are fulfilled, the diagnosis is suggested. On the basis of these criteria, LVH was diagnosed definitely by the VCG in 12 (or 60 per cent) of this series. It was probable in 4 (or 20 per cent) and was suggested in 4 (or 20 per cent). When the control or non-LVH group was analyzed in the same way, 4 (or 20 per cent) satisfied the diagnosis for LVH, 5 (or 25 per cent) were probables, 8 (or 40 per cent) were suggestive, and 3 (or 15 per cent) did not fall within the LVH criteria.

Thus, when the LVH group is compared with a group of patients of similar age who had hemodynamically insignificant valvular lesions, controlled hypertension, or who were considered normal, there is considerable overlap between the two groups. There may be several reasons for this. First, these criteria are so sensitive that specificity is sacrificed and such an overlap is inevitable. Second, all VCG studies have shown a wide range of values for normal subjects and for patients with LVH (Table IV). Such wide ranges result inevitably in some overlap between the normal and the LVH group. One is then left with the problem of where to draw a dividing line between the two groups or, putting it another way, does one wish criteria for LVH to emphasize specificity or sensitivity? When less sensitive criteria are used, many patients with established LVH, such as the patients in this study, will fall outside the limits of such criteria. Third, it is possible that some of the con

trol patients actually had a slight amount of LVH which was not detected. In this regard it is noted that the control group and LVH group had QRS angular displacement values that were similar and that the control group had QRS angular displacement values in an intermediate position between the normal groups[6,11] and the LVH groups[5,12,13] reported on by other authors. Moreover the normal groups reported on by McCall, Wallace, and Estes,[7] Murata and associates, and Hugenholtz and Liebman[11] had maximum QRS voltage values smaller than the present control group. In contrast, the normal groups reported on by Bristow[6] and Draper and associates[10] had maximum QRS voltage values larger than the present control group (Table IV).

The present criteria are useful in the diagnosis of LVH. They are sensitive and patients with moderate LVH *will fall* within the suggested criteria as well as those with more severe forms. The technique for VCG analysis employed in this study has the clinical advantage of simplicity and allows for quick analysis of each tracing.

Summary

A simple clinically applicable technique is described for the VCG diagnosis of LVH. The criteria described are sensitive and enable the clinician to diagnose LVH when the amount of hypertrophy is moderate. A plea is made for standardization of VCG techniques. Identical VCG techniques will enable valid comparison between the results of various VCG studies.

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Evaluation of ECG criteria for P wave abnormalities

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A broad notched P wave was first described by Lewis in 1914 in patients with mitral stenosis and later termed "P mitrale" by Winternitz[2] in 1935. Subsequent studies attempted quantitative definition of the "P mitrale," but only recently have experimental, diagnostic, and surgical methods been adequate to define the degree of mitral valve and left atrial involvement in patients with a P mitrale.

A prolonged P wave, the ratio P duration to PR segment greater than 1.60, and the mean P axis of +30° or more to the left[4] have been described as indicative of left atrial enlargement or hypertrophy. The recent study and recognition of the posteriorly and leftward rotated forces in left atrial enlargement have led to additional parameters more specifically indicative of this condition. These include the leftward shift of the terminal P forces in the frontal plane,[6] the duration and amplitude of the negative P deflection in lead V1,[7] and the P terminal force according to Morris and co-workers.

The normal limits for P wave parameters have been defined by several studies of large populations,[4] but there remains in the literature a wide range of quantitative definitions for abnormal P wave durations and amplitude and axis deviations.[11]

The purpose of this study is to determine

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whether or not the currently accepted types for P wave abnormalities correlate with the amount of left atrial enlargement in patients with isolated mitral stenosis.

Methods and materials

The 62 patients in normal sinus rhythm included in this study were obtained from a series of 109 consecutive cases with significant isolated mitral stenosis as observed during open heart surgery for mitral valvotomy The remaining 47 cases had atrial fibrillation (AF) Information concerning age and sex for the total group and those with normal sinus rhythm (NSR) and AF is summarized in Table I The frequency of occurrence of atrial fibrillation in each decade is presented in Table II About two thirds of the patients in NSR were in the fourth and fifth decades.

Patients were digitalized when necessary and they were considered to be compensated at the time of the preoperative evaluation An estimate of the functional capacity according to the American Heart Association classification[13] was made preoperatively Routine laboratory tests chest x ray (posteroanterior lateral and both obliques) and ECG s (12 lead) were available in all cases. An assessment of the degree of mitral stenosis, left atrial enlargement (LAE) calcification and other valvular involvement was made by direct observation at the time of surgery The ECG s obtained prior to the time of operation were selected for study These were obtained on an average of 16 days prior to surgery—in two thirds of the cases within a week.

The following ECG frontal plane pa

Table I Age and sex distribution in 109 patients operated upon for significant isolated mitral stenosis

	Total group				Male				Female			
	N	Per cent	Ave. age (yr)	Range	N	Per cent	Ave age (yr)	Range	No.	Per cent	Ave age (yr)	Range
AF	47	43 1	45 4	32–62	12	48	44 7	32 56	35	42	45 7	36–62
NSR	62	56 8	37 9	19–58	13	52	34 1	23–46	49	58	38 9	19 58
Total	109	100	41 1	19–62	25	100	39 2	23–56	84	100	41 7	19 62

AF atrial fibrillation NSR normal sinus rhythm

Table II The occurrence of atrial fibrillation (AF) and normal sinus rhythm (NSR) in 109 consecutive cases of mitral stenosis according to age in decades

Decade	NSR		AF		Total
	N	Per cent	No.	Per cent	
2	1	100	0	0	1
3	14	100	0	0	14
4	19	65	10	35	29
5	20	54	26	46	46
6	8	44	10	56	15
7	0	0	1	100	1
Total	62	56	47	44	109

rameters were obtained: maximum amplitude (in millivolts) and duration (in seconds) of the P wave, presence of notching and mean P vector (in degrees). The vectors were plotted in the hexaxial system following Grant's[11] method. The amplitude and duration of the positive and negative components of the P wave in V 1 were also determined. The negative P wave component when present was measured separately and hereafter it will be termed P'V 1.

The presence of LAE was determined by x-rays and by direct observation at the time of open heart surgery. Atrial size was expressed on a scale of 0 to 4+ enlargement. To minimize the vagaries of observer variation, they were further consolidated into 3 categories: Group A, marked LAE (3 or 4+, 28 cases); Group B, moderate LAE (1 or 2+, 28 cases); and Group C, no LAE (6 cases). The incidence and types of P wave abnormalities in these three groups were derived.

Results

The average values for the duration, amplitude and axis of the P wave in the frontal plane, the amplitude and duration of the positive and negative components of the P wave in lead V 1, the ratio P wave duration to PR segment, and the P terminal force are presented in Table III. The distribution of values for the P duration, amplitude and axis in the frontal plane are shown in Table IVA, and P'V 1 amplitude and duration in Table IVB.

The mean P wave duration was 0.12 second. Only one case had a P wave less than 0.10 second. Forty three cases (69 per cent) exceeded the commonly accepted upper limit of normal of 0.11 second, and 19 cases (30 per cent) had a P wave duration of less than 0.12 second (Table IVA). The average of the ratio P duration to PR segment duration was 2.29. It exceeded the upper limit of normal of 1.60 in 48 cases (88 per cent). Two cases (3 per cent) had a ratio less than the lower limit of 1.00.

The average P wave amplitude was 0.17 mv. In 5 cases (8 per cent) it exceeded the commonly accepted upper limit of normal of 0.25 mv (Table IVA).

The mean P vector in the frontal plane was 45° (range from +90° to −30°) (Table III). The P vector was between 30° and 60° in 53 cases (85 per cent). Six cases (10 per cent) were 15° or more to the left (Table IVA). Three cases (5 per cent) were

Table III. P-wave parameters for 62 cases of isolated mitral stenosis proved at surgery

	Average	Standard deviation	Range
Frontal plane			
P wave duration in secs.	0.12 sec.	0.013 sec.	0.08–0.16 sec
P wave amplitude in mv	0.17 mv	0.072 mv	0.05–0.30 mv
Mean P wave axis in degrees	45°	22.6	90°—30°
Lead V 1			
P duration in secs.	0.03 sec.	0.026 sec.	0–0.12 sec
P amplitude in mv	0.06 mv	0.045 mv	0–0.15 mv
P' duration in secs	0.05 sec.	0.032 sec.	0–0.12 sec
P' amplitude in mv	−0.09 mv	0.062 mv	0–−0.20 mv
Macruz and Morris criteria			
P wave dur./PR seg. dur. Macruz index. Value greater than 1.6 is abnormal.[P]	2.29	1.54	0.83–6.00
P terminal force. The product of amplitude in mm and duration in sec. of the P'V 1. A value greater than −0.03 is abnormal.[7]	−0.06	0.05	0–−0.20

Table IVA. Distribution of P wave parameters in the frontal plane for 62 patients with mitral stenosis

Duration			Amplitude			Mean axis			
Seconds	No.	Per cent	Millivolts	No.	Per cent	Degrees	No.	Per cent	Per cent
0.08–0.09	1	2	0.05	3	5	−30	1	2	
0.10–0.11	18	29	0.10	14	23	−15	0	0	10
0.12–0.13	32	52	0.15	15	24	0	3	5	
0.14–0.15	9	15	0.20	17	27	15	2	3	
0.16	2	3	0.25	8	13	30	14	2	
			0.30	5	8	45	12	19	85
						60	27	44	
						75		3	5
						90	1	2	
	62	100		62	100		62	100	100

Table IVB. Distribution of P wave parameters in Lead V1 for 62 patients with mitral stenosis

Duration			Amplitude		
Seconds	No.	Per cent	Millivolts	No.	Per cent
0.00	12	19	0.00	12	19
0.0	0	0	0.05	11	18
0.04	12	19	0.10	6	42
0.06	6	42	0.15	8	13
0.08	7	11	0.20	5	8
0.10	4	6			
0.16	1	2			
Total	62	100		62	100

75° or more to the right in these 6 cases of leftward deviation of the mean P forces it is interesting to note that the corresponding mean QRS axis was +60° or more to the right in all instances. These axis determinations were for the entire P wave without regard to initial and terminal P wave forces.

The distribution for PV1 duration and amplitude is presented in Table IVB. A posterior orientation of the terminal P vector was found in the 50 cases (81 per cent) as demonstrated by a negative P wave component in lead V1 (PtV1). The P in V1 was biphasic in 37 cases (60 per cent) entirely negative in 13 cases (21 per cent) and entirely positive in 12 cases (19 per cent). The mean duration and amplitude of the positive P deflection in V1 were 0.03 second and 0.06 mv, and the mean duration and amplitude of PtV1 were 0.05 second and −0.09 mv. The average value for the P terminal force defined[8] as the product of the PtV1 duration and the amplitude, was −0.06 (Table III).

Table V summarizes the average age and P wave duration for Groups A, B, and C and for all groups. It also summarizes the incidence of P wave prolongation according to various established limits of duration for the same groups as well as P wave notching alone and P in trile

Table V. Distribution of P wave duration and incidence of notching and P mitrale in the total and the three subgroups

	Group A		Group B		Group C		Total	
Number of cases	28		28		6		62	
Average age (yr.)	37		39		35		39	
Average P duration (sec.)	12 1		11 8		11 2		11 9	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
Distribution of prolonged P waves according to various definitions								
0.10 sec. or more	28	100	27	96	6	100	61	98
0.11 sec. or more	22	79	19	68	4	66	45	73
0.12 sec. or more	21	75	19	68	3	50	43	69
0.13 sec. or more	7	25	7	25	0		14	23
Occurrence of notching and P mitrale								
Notching	15	53	14	50	2	33	32	52
Notching plus P dur. of 0.12 sec. or more	11	39	9	32	1	17	21	34

(notched P wave 0.12 second or more). P wave prolongation of any level, P mitrale and notching were consistently more frequent in the 28 cases with marked LAE. Notching occurred in 52 per cent of the total and the P mitrale occurred in 34 per cent.

The results obtained by testing the same three groups with criteria considered more specific for LAE are presented in Table VIA. There were more P abnormalities in the patients with atrial enlargement than in those with no LAE. The only exceptions were the P terminal force and the Macruz index, both of which were almost as frequent in those with no LAE.

The criteria in order of decreasing frequency for the 28 cases with marked LAE were as follows: (1) Macruz index and P terminal force (82 per cent); (2) a PV1 of 0.06 second and −0.10 mv. in size or greater (57 per cent); (3) mean P vector in frontal plane of +30° or more to the left (43 per cent); and (4) the criterion of Arevelo and co-workers, a PV1 greater than 0.06 sec. or greater than −0.10 mv. (25 per cent). A mean P vector of +30° or more to the left was found only in those with LAE (marked or moderate). The group with no LAE is too small for a statistical comparison with one criterion. When prolongation was also included in the definition of abnormality, the differentiation between these groups becomes more evident (Table VIB). It is interesting to note that the criterion of a mean P vector in the frontal plane of +30° or more to the left remains identical in both tables (VIA and VIB), suggesting that a leftward deviation of the mean P wave forces is accompanied by a P prolongation.

The small number of patients in each decade (Table VII) precluded statistical significance of the averaged values, but several observations of the trend are of interest. There is little variation for the P duration, P amplitude, and P axis in the frontal plane from the third to the sixth decades. The mean P duration of the initial positive forces in Lead V1 increases 0.01 second for each decade.

The terminal negative forces decrease in duration in the sixth decade (Table VIII); this progressive decrease of the

Table VIA Frequency of occurrence of LAE according to currently accepted criteria

	Group A 28 cases		Group B 28 cases		Group C 6 cases		Total 62 cases	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
I PV 1 0.06 sec and −0.10 mm or greater	16	57	14	50	1	17	31	50
II PV 1 greater than 0.06 sec or greater than −0.10 mm	7	25	6	21	1	17	14	23
III P terminal force greater than −0.03	23	82	17	61	4	66	42	68
IV Mean P vector in the frontal plane 30° or more to the left	12	43	8	29	0	0	20	3
V P duration/PR seg (Macruz index) greater than 1.60	23	82	19	68	5	83	47	76

Table VIB LAE criteria plus criteria of P wave prolongation of 0.12 or more

	Group A 28 cases		Group B 28 cases		Group C 6 cases		Total 62 cases	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
I PV 1 0.06 sec and −0.10 mm or more	14	50	10	36	0	0	23	37
II P terminal force greater than −0.03	17	61	1	43	2	33	24	39
III Mean P vector in frontal plane 30° or more to left	12	43	8	29	0	0	20	31
IV P duration/PR seg (Macruz index) greater than 1.60	18	64	13	46	2	33	33	53

terminal negative forces becomes particularly manifest when the "P terminal force" is studied. The P terminal force for the total series of 62 cases (−0.06) is twice the value for the 8 cases in the sixth decade (−0.03).

Discussion

The utility of P wave analysis for the diagnosis of mitral stenosis and other diseases has been limited by the inherent observer variation,[11] the increasing incidence of atrial fibrillation in the older age groups, and a lack of agreement on the meaning of specific P wave changes. The diagnostic value of the prolonged P wave is illustrated in this study by the finding of 69 per cent of our cases with a P wave of 0.12 second or more. This is an abnormality; most normal populations rarely exceed a mean value of 0.10 second. The qualitative recognition of either a notched P wave or a diphasic or negative P in Lead V 1 (52 per cent and 81 per cent respectively on our series) makes the ECG strongly suggestive of atrial abnormalities.

The significance of P wave abnormali

Table VII. Average values for the P wave in 61 cases with mitral stenosis according to age in decades

	Decade				
	3 (*14 cases*)	*4* (*19 cases*)	*5* (*20 cases*)	*6* (*8 cases*)	*Total* (*61 cases*)
Frontal plane					
P duration (sec.)	0.12	0.12	0.11	0.13	0.12
P amplitude (mv.)	0.17	0.19	0.14	0.16	0.17
PR interval (sec.)	0.17	0.17	0.17	.22	0.17
P axis (degrees)	40°	41	51	48°	45°
Macruz index, P duration/PR seg. duration	2.57	2.93	2.42	1.54	2.50
V_1					
P duration (sec.)	0.02	0.03	0.04	0.05	0.03
P amplitude (mv.)	0.06	0.05	0.08	0.07	0.06
P′ duration (sec.)	0.05	0.06	0.05	0.03	0.05
P′ amplitude (mv.)	0.09	0.10	0.08	0.09	0.09
P terminal force	−0.06	−0.07	−0.05	−0.03	−0.06

Table VIII. Frequency of occurrence of P-wave abnormalities according to current criteria including first degree heart block

	Decade									
	3 (*14 cases*)		*4* (*19 cases*)		*5* (*20 cases*)		*6* (*8 cases*)		*Total* (*61 cases*)	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent	N	Per cent
P duration 0.12 sec. or more	9	64	12	63	12	60	8	100	41	67
P duration/PR seg. duration 1.60 or more	10	71	16	84	17	85	3	38	46	75
P′V1 0.06 sec. or more and −0.10 mm. or more	7	50	11	57	11	55	2	25	31	51
P terminal force greater than −0.03	10	71	15	79	12	60	3	38	40	66
PR interval 0.20 sec. or more	1	7	2	11	2	10	6	75	11	18

ties in a patient with mitral stenosis should be assessed in conjunction with clinical data such as the onset and duration of the disease, the progression of cardiac and pulmonary symptoms, and x-ray findings. P wave abnormalities are a reflection of three variable factors: (1) progressing atrial myocardial degeneration, (2) left atrial enlargement, and (3) disturbances of atrial depolarization. These three factors are so interrelated that their independent assessment is probably unjustified.

The term *intra-atrial block*[3, 11] has been proposed to explain notched P wave of 0.12 second or more as a more suitable

term than "P mitrale" which implies a specific valvular disease. This notching occurred in 4.5 per cent of a series of 4,500 routine hospital ECG's. The associated findings in those patients included hypertension, coronary artery disease, rheumatic and syphilitic heart disease and digitalis and quinidine therapy.

No specific atrial conduction pathways have been clearly demonstrated in man.[14] The status of the conduction medium (atrial myocardium) is probably the determining factor in the P wave duration and morphology. Simultaneous esophageal and limb leads, as well as direct atrial ECG's[7, 8] support the hypothesis that the P wave prolongation and notching represent the decreased conduction velocity in a degenerated myocardium which may be ischemic, fibrotic or hypertrophied. Reynolds[9] described an asynchrony of 0.05 second between the initial right and terminal left forces in left atrial disease; he suggested that a decrease in amplitude of the P wave represented a severe myocardial involvement. Evidence contrary to this observation was found in a study by Soloff and Zatuchni.[21] The rate of progression of the disease is mostly influenced by the duration and the degree of hemodynamic stress.

Recent studies have demonstrated a relationship between the posteriorly directed terminal P forces as manifest by the negative deflection of the P in Lead V 1 (PTV 1) and the presence of left atrial enlargement.[7, 19, 21, 22] This was suggested by our study; criteria tested for LAE had a greater incidence in the group with LAE than in the group with no LAE (Table VIA). Abnormalities indicative of LAE have been noted in severe aortic stenosis,[23] left ventricular hypertrophy,[22] and hypertension,[24] and many of these represent changes in atrial dynamics rather than size per se.

An increase in the amplitude of the negative component of the P wave in V 1 has been suggested as a good indicator of early congestive heart failure.[25] In cases with an enlarged left atrium a characteristic widening of the vector loop in the horizontal plane is found. As the left atrial conduction velocity decreases the asynchrony between the right and left atrial events becomes apparent. This is particularly well seen in Lead V 1 with forces in leftward and primarily posterior direction.[26] No correlation between LAE and P duration, amplitude or notching was found by Soloff and Zatuchni;[21] the same authors found a good correlation between the PTV 1 and the left atrial volume. The incidence of an abnormal PTV 1 was high in our series of 28 cases with LAE.

The mean P axis may accompany the rightward shift of the mean QRS axis upon development of right ventricular hypertrophy; it may also shift to the left reflecting enlargement of the left atrium when the left atrial forces become predominant because of atrial hypertrophy or dilatation; this leftward deviation may be observed only when the axis of the terminal portion of the P wave in the frontal plane is plotted. Soloff and Zatuchni found a correlation of LAE to the posterior shift of the mean P axis, but they could determine no relationship of LAE to left axis deviation of the mean P vector in the frontal plane.

Conclusions from analysis of Macruz indices (P duration/PR interval) are limited by the effects of digitalis in many of the patients in whom this drug is employed.

According to our data, analysis of P wave abnormalities does not differentiate moderate from marked LAE; moreover, these changes may be seen with no LAE. This is in accordance with the work of Peters, Morris and McIntosh[19] who found no association between left atrial size (by x ray) and electrocardiographic data. All of the described P changes might be more appropriately termed "atrial overload," "atrial strain" or "atrial abnormality" because these changes may be found regardless of whether or not there is an increase in size of the atrium.

Summary and conclusions

The preoperative electrocardiograms of 62 patients with isolated mitral stenosis proved at open heart surgery were studied for P wave abnormalities. The average age was 38.3 years. Thirteen (21 per cent) were male and 49 ( ) per cent) female. Left atrial enlargement was defined by x ray and by direct observation at th

time of surgery. The series was divided into 28 cases with 3- or 4-plus LAE, 28 cases with 1- or 2-plus LAE, and 6 cases with no apparent LAE. Currently used criteria for P wave abnormalities were tabulated in each of these three groups.

Although there is a tendency for P abnormalities to occur more frequently with the larger left atria, these P changes are not related to size alone. Because P wave changes similar to those in left atrial enlargement may be found in patients with normal atrial size, the term "left atrial abnormality" is more accurate in describing these P changes.

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Experimental and laboratory reports

Biplane cineangiographic determinations of left ventricular function: Pressure-volume relationships

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Arvidsson[1] in 1958 described a method for determining the volume changes of both the opacified left atrium and ventricle with a biplane radiographic technique. The x-ray equipment had the capability of 6 film pairs per second. Therefore, in order to construct a volume curve, it was necessary to integrate the volume measurements obtained over several cardiac cycles. Dodge, Hay, and Sandler[2] using a similar biplane radiographic technique studied the pressure and volume relationship of the left ventricle in both the normal and diseased state. Chapman and associates recognized the desirability of faster filming speeds and developed a cinefluorographic unit whereby the image projected on 35 mm. cameras at speeds of 15 or 30 frames per second. Since image intensification was not used in this system, the radiation levels necessary to obtain adequate detail were excessive. This potential hazard restricted the use of the unit to studies of animals and selected patients. These studies and those of Bunnell, Grant, and Greene[4] and Miller, Kirklin, and Swan[5] have emphasized the usefulness of the technique for studying cardiac dynamics.

With image intensification it is possible to obtain high quality films of the opacified ventricle at a speed of 60 frames per second without serious radiation hazards. A biplane image intensifier cinefluorographic unit therefore was specially constructed so that volume measurements could be made at this speed. Sixty such measurements per second, embracing several cardiac cycles, permit accurate construction not only of a volume curve for a given cardiac cycle but curves of consecutive cycles. This report describes in detail this unit, the technique for calculating ventricular volumes from such radiographic observations, and the integration of the volume data with simultaneous pressure measurements for the construction of pressure-volume loops.

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Methods

Equipment. Two high resolution 9 inch input phosphor 3 inch output phosphor image intensifier systems were joined in a vertical and horizontal relationship above an x-ray table the top of which had two-directional horizontal travel. The image tubes were carefully selected to avoid excessive spherical distortion and matched for gain. Flexibility in mounting the tubes enabled easy positioning of the patient. For the average adult patient the distance from the focal spot of the vertical x-ray tube to the intersect of the central beam of the horizontal tube was 69 cm.; the distance from the focal spot to the center of the front plate of the vertical image intensifier housing was 77 cm. These distances for the horizontal tube were 82 and 100 cm., respectively. Filming was accomplished by Photomechanism cameras with variable speeds up to 60 frames per second using 35 mm. Double X panchromatic negative safety film.† Satisfactory filming of the average adult at these speeds required about 20 Ma. and 100 kv. for each tube. The x-ray tubes were pulsed by the cameras only when the film travel had been completed and the shutter of the camera was open. In addition, an electronic shuttering device for each image intensifier tube was added to decrease scatter radiation and fogging of the alternate right angle film. This resulted in the film pairs being out of phase by 8.3 milliseconds. The exposed 35 mm. film was developed using ethol Single Mix/90 developer‡ and subsequently reduced and copied as a 16 mm. print by a modified Uhler copier and reducer.§ The films were then analyzed with a modified Kodak Analyst 16 mm. projector.

An electronic device, with moveable lead-tipped plastic rods, was constructed to permit synchronization of the individual frames of both planes with the recorded physiologic data. A moveable lead-tipped rod was positioned in front of each image tube so as to be visible on the biplane film. The R wave of each QRS complex triggered a square wave impulse from a trigger channel in the Electronics for Medicine DR 8 Recorder. This impulse initiated movement of the lead-tipped plastic rods and inscription of a square wave on the photographic record. The onset of a specific QRS complex could then be identified both on the biplane films and the photographic record. The electronic and mechanical delay of this system was approximately 65 milliseconds, a time interval equivalent to 2 frames of film at 30 frames per second and 4 frames at 60 frames per second. Adjustment for this delay was made in the timing of subsequent calculations.

Postmortem heart studies. Thirteen adult hearts were prepared by opening the left atrium and suturing tightly together the mitral valve. After the aorta was transected above the coronary arteries, the initial 1 cm. of each coronary vessel was dissected free. A large Kelly clamp was placed beneath the vessels and around the aorta at the level of the sinuses of Valsalva. A No. 15 gauge blunt needle was inserted into the left ventricle through the aortic valve and the clamp approximated. Each heart was placed on a pillow 12 cm. above the x-ray table top and positioned similar to in vivo relationships for both the horizontal and vertical tubes. Air trapped within the closed ventricle was aspirated through a small needle inserted at the apex. Thirty cubic centimeters of barium sulfate paste were injected through the needle into the left ventricle. A short strip of film was exposed in both planes at 60 frames per second. Five or 10 c.c. increments of barium paste were injected into the chamber and filmed in both planes until leakage occurred at the mitral or aortic valve. This procedure was repeated for each of the 13 hearts. A total of 97 different film pairs over a range of 30 to 150 c.c. were obtained from the 13 hearts. After completion of filming and without moving the image tubes, each heart was replaced by an aluminum bar measuring 8 × 2 × 2 cm. which was also filmed in biplane. The projected image of the bar was subsequently used to correct for magnification.

VENTRICULAR VOLUME CALCULATIONS. The 16 mm. biplane film was displayed on a

*Rowe Manufacturing Division, Picker X-Ray Corporation, Cleveland, Ohio.
†Eastman Kodak Company, Rochester, N. Y.
‡Plymouth Products Company, Chicago, Ill.
§Uhler Cine Machine Company, Detroit, Mich.

screen and the screen to-projector distance was adjusted to restore the projected image of the aluminum bar to the original size 8 X 2 cm This maneuver also served to restore the projected image of the opacified left ventricle to its original size. As the x ray source-object image tube distances were different in the two planes it was necessary to adjust the screen to-projector distance for both the horizontal and verti cal films.

The image of the opacified left ventricle w is traced onto paper from the biplane film pairs for each known volume The clamp which had been approximated at the sinuses of Valsal 'a was considered to be the base of the aorta Two measurements were obtained from each traced image (1) the longest length of the chamber (2) the area as determined by plani metry The diameter D of the image was calculated from the formula for an ll pse

$$D = \frac{4A}{\pi l}$$

where
A = planimetered area of th ventricular chamber
l = longest measured length of the chamber
π = 3 14

After calculation of the diameters for both the anteroposterior (AP) and lateral (Lat) images left ventricular volume (V) was calculated from the volume formula for an ellipsoid

$$V = \frac{4}{3} \pi \frac{L}{2} \frac{D_{AP}}{2} \frac{D_{Lat}}{2}$$

where
L = longest measured length from either the anteroposterior or lateral image
D_{AP} = calculated diameter of the nteroposterio chamber image
D_{Lat} = calculated diameter of the later hamber image.

In this manner the left ventricular volume of the heart for eacl known mount

Table 1 The hemodynamic and angiocardiographic data

Patient	Diagnosis	Cardiac output (L/m)	Heart rate (per min)	Stroke vol me ( )	Mea aortic arterial pressure (mm Hg)
L. L. 49-y ar-old wh female	No h lar disease	4 70†	90	52 2	136
C F 18-year old whit female	Patent ductu arteriosus and entricular septal defect	4 38‡ (systemic) 7 00* (pulmonary)	85	51 5 (systemic) 82 3 (pulmonary)	92
D R. 16-year-old wh t female	Aortic insufficiency	4 02‡	108	37 0	81
J H 31 year-old wh t male	Aortic insufficiency and aort tenosis	4 55‡	80	57 0	95
M C. 32-year-old wh t female	H pertrophic subaortic tenos nd mitral insufficiency	5 07‡	96	53 0	9
W B 3 year-old white male	C nstricti pericard'tis nd effusion with mitral insufficiency	3 70*	109	29 6	95

Determined from cardiac output and heart
†Dye-d lu cardiac output
‡F k cardiac output

of barium sulfate past was calculated A regression equation was determined for the relationship between the calculated and each of the 97 known volumes as shown n Fig 1 The standard error of est mate was ± 5 6 c.c. and the correlation coefficient was 0 986

Patient studies The 6 patients in this report (Table 1) had right and left heart catheterizations by previously described techniques. Cardiac outputs were measured by the dye-dilution technique in Patients L. L. and W B and by the Fick method in Patients C E. D R J H and M C The two methods have been demonstrated to agree closely in this laboratory

Prior to obtaining the ventriculograms, the horizontal and vertical x ray units were positioned about the supine patient so that the left ventricle was at the center of the field for both image tubes The electrocard ogram the radial artery and left

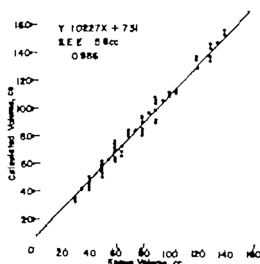


Fig. *1* Ninety-seven volume calculations were compared with know volume measurements in 13 postmortem heart studies in ad lts. The volumes ranged from 30 to 150 .c. *S.E.E* = Standard error estimat = orrelation coefficient

Angiocardiographic					Left ventricular work	
End diastolic volume	*End systolic volume c.c.*	*Left ventricular stroke volume c.c.*	*Regurgitant flow or Shunt flow c.c.*	*Left ventricular cardiac output L./min.*	Stroke work (Gm. M.)	Pressure-volume work (Gm. M.)
74 5	19 5	55		4 29	101 8	99 8
125 0	46 0	79	27 5	8 37	68 0	94 7
274 0	128 0	146 0	109 0	14 89	44 6	227 8
132 0	22 0	110 0	53 0	8 58	77 7	193 4
120 0	30 0	90 0	38 0	8 10	68 6	169 7
72 0	29 0	43 0	13 4	4 39	40 8	57 7

ventricular pressure and the square-wave of the trigger channel were recorded by the Electronics for Medicine recorder at a paper speed of 100 mm per second. The power injector and pressure transducer were connected to the left ventricular catheter (8 F Gensini) by a three-way stopcock with a Luer connector permitting left ventricular pressure to be recorded by a Statham P23Db strain gauge until immediately prior to the injection of contrast medium. The ventriculograms were obtained with the patient at full inspiration. Biplane filming was performed at 30 frames per second in Patient L. L. and 60 frames per second in the remaining 5 patients. Immediately after the appearance of the anteroposterior and lateral images on the television monitors, the circuit of the electronic marker was activated. The occurrence of the R wave of the next and subsequent QRS complexes was therefore indicated on both the biplane film and the photographic record as described above. After visualizing the movement of the rods on the television monitors, 35 to 50 c.c. of Angio-Conray* (sodium iothalamate 80 per cent) contrast medium were injected into the left ventricle by a Talley power injector† at a pressure of 400 pounds per square inch. Filming was continued until the left ventricle was cleared of contrast medium. Upon completion of the catheterization and removal of the patient from the laboratory the image tubes were repositioned precisely as in the patient study. The aluminum bar was placed on a pillow centered for both image tubes and filmed in biplane.

VOLUME CURVES AND PRESSURE-VOLUME LOOPS. The films of each biplane pair were traced with particular attention to identify the base of the aorta by the position of the sinuses of Valsalva. The volumes were calculated as described for the postmortem heart studies and corrected by the regression equation derived from the postmortem ventricular volume data

where

$V_c = 0.978\, V_{cal} - 7.15$

V_c = corrected ventricular volume

V_{cal} = calculated volume from biplane film pair

*Mallinckrodt Pharmaceuticals, St. Louis, Mo.
†T. Rey Anaesthetic Equipment, Ltd., London, England

These individual volume measurements were plotted sequentially and connected by a line of best fit. At a film speed of 30 frames per second a volume observation was made every 33.3 msec. and at 60 frames per second every 16.7 msec. The initial movement of the lead tipped marker was identified on the biplane film and after correction for the inherent delay of the system related to the onset of the QRS complex. Left ventricular volume changes could then be related to left ventricular pressure changes with time common to both.

The systemic arterial pressure and heart rate did not change during the injection of contrast medium and biplane filming in these patients. Therefore the left ventricular pressure was assumed to be unchanged from control pressure. This was confirmed in Patients W. B. and D. R. in whom the left ventricular pressure was recorded during the filming. As the patients selected for this report maintained normal sinus rhythm with similar R-R intervals the left ventricular pressure contour prior to injection was related to the volume curve by the onset of the QRS complex. A pressure-volume loop beginning with the onset of the QRS complex was then constructed by plotting each volume observation corrected to the line of best fit and the corresponding pressure coordinate.

STROKE WORK AND PRESSURE-VOLUME WORK. Mechanical work is the result of moving a given mass through a given distance. When pressure moves a fluid, work may be defined as the integral of pressure and change in volume. Conventionally external work of the left ventricle has been determined from stroke volume and mean aortic systolic pressure

$$SW = SV \times \bar{P} \times 1.36 \times 10^{-2} \times 1.055$$

where

SW = stroke work (Gm.M. per beat)

SV = stroke volume (c.c. per beat) determined from cardiac output and heart rate

$\bar{P}$ = mean aortic systolic pressure (mm. Hg)

1.36×10^{-2} = factor for conversion from mm. Hg to Gm.M.

1.055—specific gravity of blood

Since the pressure-volume loop of the left ventricle represents pressure and volume changes for a single cardiac cycle

the loop is a measure of left ventricular pressure volume work. The area beneath the ejection portion of the loop indicates the work of the left ventricle in ejecting blood

$$PVW = PA \times 1.36 \times 10 \times 1.055$$

where

PVW = pressure-volume work, Gm.-M per beat
PA = area beneath the ejection portion of the pressure volume loop in cm. multiplied by the scale factors for pressure and volume.

In this study only potential work is included in the calculation of stroke work. In the resting state kinetic work has been shown to range from 0.9 to 3.5 per cent of the total work of the left ventricle. Snell and Luchsinger demonstrated that the kinetic or accelerative work can be ignored as it represents less than 2 per cent of the total work.

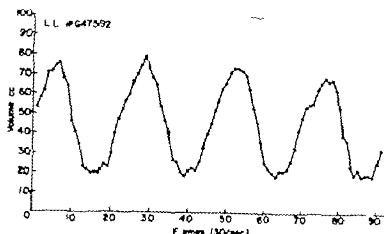
Results

Left ventricular stroke volume. Observations from 6 patients with a variety of pathophysiologic abnormalities who maintained stable heart rates and pressures during the cinefluorograms were selected for discussion (Table I). Representative end systolic and end diastolic biplane frames from the study of Patient L. L. are shown in Fig. 2. This patient had no valvular disease or intracardiac shunt. Continuous volume curves from four consecutive cardiac cycles in regular rhythm are displayed in Fig. 3. The left ventricular stroke volume calculated as the difference between the end diastolic and the end systolic volume was 55, 60, 54, and 50 c.c. (average of 54.7 c.c. per beat, Table II). The forward stroke volume, calculated from the cardiac output and heart rate was 52.2 c.c. (Table I).

Patient C. E. had a small ventricular



Fig. 2. Biplane film pairs. Illustrated are representative frames from the biplane film in the anteroposterior (left) and lateral projections (right) during diastole (upper) and systole (lower). The dotted lines demonstrate the manner in which the opacified chamber was traced onto paper.



I ig 3 Seque tial lu me letermi nations The entric lar ol ie me surement during fo nsecutive ar iac cycles p tien w hout alvular heart dise se re illustrated The lef entric lar stroke ol mes f r these four les are 55 60 54 nd 50 respectivel er ge 54 7 per be The film ng speed w 30 f mes per se n l

T ible II I he angiographic volume dat i in 2 patient without valvular heart dise se

P tient	C l	End d astol olume ( )	End s stol ol me ( )	Left vent ula strok ol m ( )
I I	1	74 5	19 5	55 0
	2	79 0	19 0	60 0
	3	72 5	18 5	54 0
	4	69 5	19 5	50 0
	M	73 8	19 1	54 7
C J	1	1 5 0	46 0	79 0
	2	126 0	44 0	82 0
	M	125 5	45 0	80 5

septal defect and i p t ent luctus rteriosus. There wa no arteri l unsaturation indicating the absence of significant righ t-to-left shunt In the presence of a left-to-right shunt t or beyond the entricul r level the total olume of blood ejected from the left entricle i the sum of the systemic stroke volume and the shunt flow per beat Consequently the left ventricular stroke volume should equ l the pulmonary blood flow per be it a de termined by the Fick method The left entricular stroke olume determined by angiocardiography for two consecutive beats was 79 and 82 c respectivel (Table II) the pulmonary blood flow was 83 c c per beat (Table I)

The remaining four p tient n thi study h d v rying degrees of l ul r insufficiency (Table I) As described by Sandler and associates the reg rg itant volume per beat w calcul ted s the difference in left ventricul r stroke olume determined b the ngiogr ph c ethod and the forward troke volume determined from the card ic output (T ble I) Regurgitant flow per be t r nged fro 13 c c in the patient with peric rdi al d se se to 109 c c in the patient with severe aortic insufficiency

The left entricular output per i inute c lculated as the product of ang graph c stroke volume and the he rt r te anged from 4 9 liter per m nute in tl tient

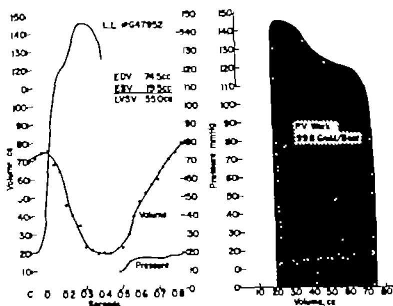


Fig. 4. The pressure and olume data (left) and pressure olume loop (righ) in patient without lar heart disease. As seen the panel on the left, the end diastolic olume EDV is normal t 74.5 although the diastolic pressure is elev ted. The end stolic olume, ESV is 19.5 nd the left entricular troke olume $LVSV$ is 55. The pressure- olume loop is seen the panel on the righ. The left entricular pressure- olume ork PV ork is indic ted by the lined rea.

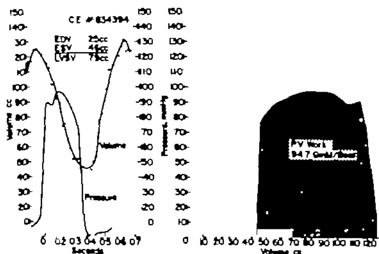


Fig. 5. The pressure and olume data (lef) and pressure olume loop (righ) pa ient w th entric lar septal defec nd paten duct rteriosus. Note the panel on the left, that the end diastolic ol me nd pressure are normal. I be pressure- olume loop the right the period of isovolumic contraction represented by the scending limb demonst tes loss of entricular olume prior the opening of the aortic al e. During isovolum relaxa on represen ed by the descending limb here is on inued loss of olume after losure of he aort l.

w thout anatomical disease of the left entricle to 14.99 l t rs per minut in the patient with aortic insufficiency.

Left vent icula wo k. Left ventricula pressu e and volume curves of the 6 se lected pa tients are shown n the left panel of Figs. 4 through 9. The pressure and vol me coord nates plotted sequentially on the right side of each illustration to lescribe the pressure vol me loop. Th

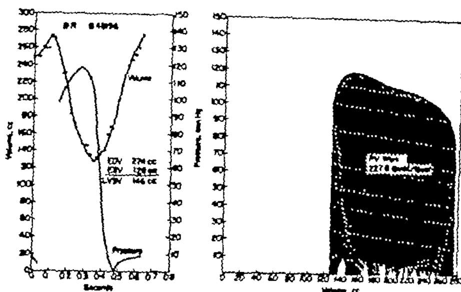


Fig 6 The pressure and volume data (left) and pressure-volume loop (right) in a patient with mixed aortic insufficiency As seen in the panel on the left the end diastolic volume is 274 cc and the end diastolic pressure is within normal limits. The pressure-volume loop on the right demonstrates that ventricular filling begins at the time of aortic valve closure and continues throughout isovolumic relaxation as well as during the period of diastolic filling The ventricle continues to fill during ventricular systole as demonstrated by the early rightward deviation of isovolumic contraction

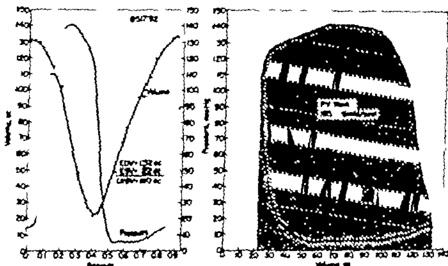


Fig 7 The pressure and volume data (left) and pressure-volume loop (right) in a patient with moderate aortic insufficiency and mild aortic stenosis. The pressure-volume loop as seen in the panel on the right demonstrates an increase in volume during isovolumic relaxation, indicating aortic insufficiency The gradual loss of volume during isovolumic contraction indicates mild mitral insufficiency although it is not clinically evident

shaded area beneath the ejection portion of each loop indicates the systolic pressure volume work of the left ventricle. In Patient L. L., in whom there was no valvular abnormality of the left ventricle stroke work calculated from the dye-dilution data and pressure volume work calculated from the angiographic data were 101 8 and 99 8 Gm M per beat respectively (Table I) In Patient C. E. with the ventricular septal defect and a patent ductus arteriosus, stroke work calculated from the forward Fick output of 4.38 liters per minute was 68 Gm M per beat pressure-volume work

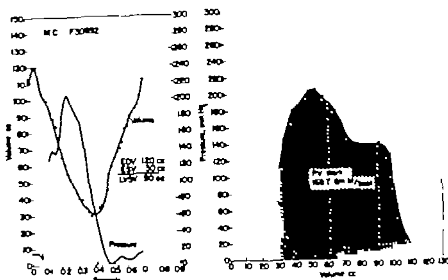


Fig. 8. The pressure and volume data (left) and pressure-volume loop (right) in patient with hypertrophic subaortic stenosis and mitral insufficiency. The loss in ventricular volume during the early phase of isovolumic contraction, as represented by the doubling back of the pressure-volume loop, suggests abnormal closure of the mitral valve resulting in mitral insufficiency. The rate of systolic ejection into the aorta is extremely rapid in the early phase of the period of systolic ejection. The area beneath the diastolic filling limb of the pressure-volume loop is measure of the diastolic work or the work done on the ventricle during filling.

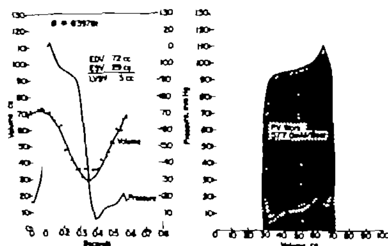


Fig. 9. The pressure and volume data (left) and pressure-volume loop (right) in a patient with constrictive pericarditis, pericardial effusion, and mild mitral insufficiency. The mitral insufficiency occurs during the period of systolic ejection and is due to the transseptal catheter lying across the mitral valve (see text). The area beneath the diastolic filling limb of the pressure-volume loop again indicates the increased work necessary to fill the ventricular chamber.

calculated from the angiographic data was 94.7 Gm.M. per beat. The difference in stroke work and pressure-volume work, 26.7 Gm.M., indicates the work of left ventricle in shunting blood across the defects during each cardiac cycle.

In the remaining 4 patients, with varying amounts of valvular insufficiency and/or stenosis, stroke work ranged from 40.8 to 77.7 Gm.M. per beat. It is assumed that in each of these patients the difference between pressure-volume work and stroke work represents the work expended because of the valvular insufficiency and/or stenosis and varied from 16.9 Gm.M. per beat to 18.3 Gm.M. per beat.

Discussion

The clinical studies described in this report add further support to the accuracy of the radiographic method for determining ventricular volume.[22] A comparison of the stroke output calculated both by the angiographic and the conventional methods demonstrated excellent correlation in the two patients without valvular insufficiency. The advantages of analyzing cardiac dynamics by means of the construction of a pressure volume loop have been demonstrated by Arvidsson, Dodge, Hay and Sandler and Bunnell, Grant and Greene. These investigators constructed pressure-volume loops by integrating the data from several successive cardiac cycles. Chapman, Baker and Mitchell employed cinefluorography to describe the pressure volume relationships of a single cardiac cycle in animals during rest and exercise but only limited studies were performed in man. The pressure volume characteristics of individual cardiac cycles in various heart diseases are described and analyzed in this report.

Pressure volume loops not only graphically describe the pressure and volume relationships throughout the cardiac cycle but also illustrate disturbances in left ventricular function. The contour of a normal pressure-volume loop is demonstrated in Fig 4. The right side or ascending limb represents the period of isovolumic contraction which describes that interval of the cardiac cycle between closure of the mitral valve and opening of the aortic valve. Although undergoing a rapid rise in pressure the left ventricle is a closed chamber during this period. When the left ventricular pressure exceeds the diastolic pressure in the aorta the aortic valve opens initiating the period of systolic ejection. This phase of the cardiac cycle is represented by the superior aspect of the pressure-volume loop. As the rate of the left ventricular ejection slows, the pressure falls and the direction of the loop turns downward. When the left ventricular pressure falls below the aortic pressure the aortic valve closes. Isovolumic relaxation follows represented by the continuation of the descending limb on the left side of the figure. The aortic and mitral valves are both closed during this phase of the cardiac cycle. Although pressure is falling there is no change in volume. This period is terminated by the opening of the mitral valve. The loop is completed by the inferior limb which represents the diastolic filling period.

The period of isovolumic contraction can be altered by a ventricular septal defect or by mitral incompetence as illustrated in the pressure-volume loops in Figs. 5 and 8. Since the left ventricle is undergoing a volume change during this period it is not truly isovolumic. Although patient J. H. (Fig 7) had no clinical evidence of mitral insufficiency, the early loss in volume during the period of isovolumic contraction suggests a small amount. Minimal mitral regurgitation apparently due to the catheter crossing the mitral valve was demonstrated cinefluorographically in patient W. H. Nevertheless the period of isovolumic contraction of the pressure volume loop appears normal (Fig 9). It is suggested that the mitral valve was anatomically normal. Therefore the regurgitation did not occur during this period but later in systole at a time when the valve distorted by the catheter was stressed by the high pressure of left ventricular ejection. On the other hand in patient M. C. (Fig. 8) with hypertrophic subaortic stenosis, demonstrated mitral regurgitation coincident with the onset of ventricular contraction followed by a relatively normal completion of the period of isovolumic contraction. This finding suggests abnormal closure of the mitral valve possible on the basis of papillary muscle dysfunction. The filming speed of 60 frames per second supplies a sufficient number of volume observations to permit one to make this speculation. The duration of isovolumic contraction as indicated by the number of volume observations included in this limb of the loop may also provide information concerning the dynamics of cardiac function. For example the period of isovolumic contraction is prolonged in patients with ... per... ten... and ... result ... insufficiency.

The ejection portion of the pressure-volume loop is abnormal in patients with obstruction to left ventricular outflow (Fig. 7 ... In ... the ...

an incompetent mitral valve or through a ventricular septal defect may continue during this phase of the cardiac cycle without appreciable altering the contour of the loop.

The period of isovolumic relaxation is altered by aortic insufficiency. It can be seen in Figs. 6 and 7 that significant filling of the left ventricle occurred after the time of aortic valve closure during the early part of this period. On the other hand there is a continued loss of volume during this period in the patient with the interventricular septal defect (Fig. 5) due to continued left-to-right flow through the defect. This phase of the cardiac cycle may be shortened by the presence of an elevated left atrial pressure causing an earlier opening of the mitral valve.

The diastolic filling period describes both the volume accepted by the chamber and the pressure changes resulting from this increase in volume. This relationship may be altered by changes in the distensibility of the myocardium or pericardium. The ratio of changing volume to changing pressure is an expression of the compliance of the ventricle. Patient D. R. with severe aortic insufficiency had a large end diastolic volume without an increase in filling pressure (Fig. 6). Patient W. B. with pericarditis and effusion (Fig. 9) and Patient M. C. with left ventricular hypertrophy (Fig. 8) had smaller end diastolic volumes but higher filling pressures. The slope of the diastolic limb in the latter 2 patients indicates an increased resistance to left ventricular filling. Patient L. L. had no detectable heart disease and a normal left ventricular end diastolic pressure early in the cardiac catheterization. However the diastolic pressure rose progressively during coronary arteriography which required a total of 200 c.c. of Hypaque M (sodium and methylglucamine diatrizoates, 75 per cent). The ventricular volume study was then carried out after the elevation of diastolic pressure had developed as is evident in the diastolic limb of the pressure volume loop (Fig. 4). The injection of large volumes of contrast medium is known to increase the circulating blood volume. Whether the elevated diastolic pressure was due to this or other factors is unknown.

Ventricular filling in Patient D. R. (Fig. 6) was particularly interesting. The ventricle filled not only by inflow from the left atrium but also by retrograde flow from the aorta. The latter began at the time of closure of the incompetent aortic valve and continued throughout the periods of isovolumic relaxation and diastolic filling. In addition the ventricle continued to fill during the period of isovolumic contraction of the ensuing cardiac cycle. This filling as demonstrated by the ascending limb of the pressure-volume loop was observed to continue until the aorticoventricular gradient was abolished at 55 mm. Hg. This was in fact the aortic diastolic pressure. Dressler and Rubin reported 2 cases of aortic insufficiency in which this overlapping of ventricular filling and ventricular systole was demonstrated by phonocardiography and apex cardiography.

The area beneath the ejection portion of the pressure volume loop is an expression of the left ventricular pressure-volume work for ejection. In Patient L. L. (Fig. 4) a patient without valvular heart disease or shunts the left ventricular pressure volume work is comparable to stroke work calculated by conventional methods as described previously. However in the presence of valvular stenosis and/or insufficiency and certain left-to-right cardiac shunts, such as a ventricular septal defect or patent ductus arteriosus, the left ventricular pressure-volume work becomes more informative than stroke work. These conditions increase the pressure volume work of the left ventricle although this cannot be measured by the conventional laboratory techniques for calculating stroke work.

The area beneath the diastolic limb of the pressure-volume loop is the work performed on the left ventricle for filling. Diastolic pressure volume work may be increased by a large volume filling the chamber as in severe aortic insufficiency (Fig. 6), by pericardial disease (Fig. 9), myocardial hypertrophy (Fig. 8) or possibly by an increase in blood volume (Fig. 4).

These studies indicate the value of pressure volume loops in analyzing cardiac

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function Left ventricular stroke volume can be accurately measured in the presence of valvular insufficiency and left-to-right shunts. The alterations of the systolic and diastolic isovolumic periods in mitral and aortic valvular insufficiency can be illustrated by the rapid cinefluorographic filming technique The pressure volume loops provide a more accurate estimate of left ventricular systolic work in patients with valvular heart disease or left-to-right shunts than do conventional methods. The measurement of ventricular volume in patients with heart disease will permit additional understanding of the hemodynamic abnormalities.

Summary

A biplane cineangiocardiographic technique with filming speeds of 30 or 60 frames per second is described to estimate the instant-to-instant changes of left ventricular volume in man The results of postmortem studies in 13 human hearts and in 6 patients with various forms of heart disease are presented

Ninety seven volume observations were made in the 13 postmortem hearts over a volume range of 30 to 150 c c The volume calculations were based upon the assumption that the chamber could be mathematically represented by the formula for an ellipsoid The standard error of estimate was ± 5 6 c c and the correlation coefficient was 0 986

The angiographic left ventricular stroke volumes in a patient without anatomic left ventricular disease were 55 60 54 and 50 c.c an average of 54 c c per beat This compared favorably with the dye-dilution stroke volume of 52 2 c c per beat A second patient with a ventricular septal defect and patent ductus arteriosus had consecutive angiographic stroke volumes of 79 and 82 c c an average of 80 5 c c per beat This compared favorably to the pulmonary blood flow of 82 c.c. per beat determined by the Fick method The remaining 4 patients had valvular insufficiency and/or stenosis. The regurgitant flow per beat ranged from 13 to 109 c.c

Pressure and volume were related for the construction of pressure volume loops and the determination of the left ventricular pressure-volume work for ejection The hemodynamic significance and changes in the contour of the loops in the various pathophysiologic states are described The pressure-volume work was determined from the loops and compared to the stroke work calculated from conventional laboratory techniques. The determination of the pressure-volume work was demonstrated to be more informative than the conventional calculation of stroke work The clinical application of ventricular volume measurements will provide additional information concerning the left ventricular hemodynamics of the normal and diseased state

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The effect of diphenylhydantoin (Dilantin) and quinidine on left ventricular function in dogs

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Dall T x

In 1950 Harris and Kokernot[2] demonstrated that Dilantin was effective in the control of ventricular tachycardia associated with acute myocardial infarction in dogs. Subsequent clinical reports[3-6] attested to its usefulness in a variety of arrhythmias. However evaluations of its direct effect on cardiac performance have suggested little or no effect[7] or a deleterious effect[1] on ventricular function.

The present study was designed to isolate the myocardial effect of Dilantin by utilizing dog preparat on in which aortic flow aortic pressure nd heart rate could be controlled. The administration of Dilantin simul t of the dose and mode recommended for the tr tment of clinical arrhythmia [illegible] the dose found necess y t onvert [illegible] nd digitalis-induced arrhythmias [illegible] Lang and [illegible] Since rep ted intravenous adm[illegible] trati n h been dvocated b som [illegible] the eff t of first and second injection w s compared. Finally the effect of Dilant n on ventricular function was compared to that of quinidine administered under identical circumstances.

Methods

Mongrel dogs were anesthetized with thiopental sodium followed by chloralose (50 to 100 mg per kilogram) in propylene glycol. Respiration was maintained by a Harvard pump and blood pH and pCO_2 were monitored.

The experimental model is shown in Fig 1. The trachea was cannulated and both vagi were sectioned in the midcervi al region in some of the dogs. The chest w s opened the thoracic aorta bisect d and metal c nnul were secured in the proximal and dist l segm nt. The left ventricle ejected blood through the proximal cannula p t a Starling resistance into a reservoir filled with blood from donor dogs. The blood w s returned b a rotor pump through a heat exchanger into the distal cannulated thoracic aorta. Both common arotid arteries were cannulated nd connected with the xtra rpore l

[illegible]

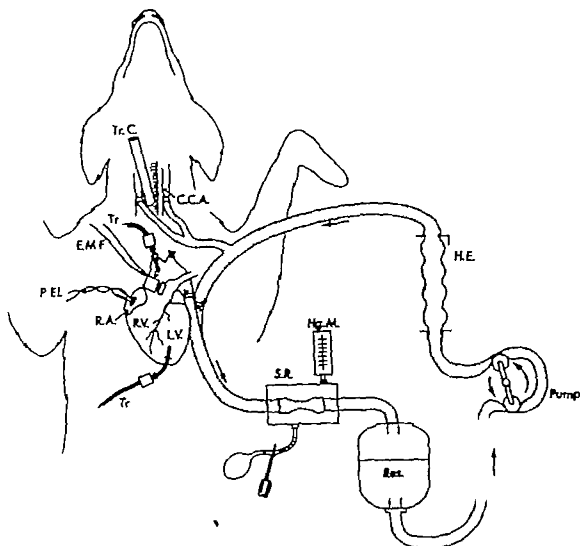


Fig. 1. Schematic diagram of preparation. *T. C.*, tracheal cannula; *C.C.A.*, common carotid artery; *R.A.*, right atrium; *R.V.*, right ventricle; *L.V.*, left ventricle; *S.R.*, Starling resistance; *Hg.M.*, mercury manometer; *Res.*, blood reservoir; *Pump*, rotor pump; *H.E.*, heat exchanger; *T.*, pressure transducer; *E.M.F.*, electromagnetic flowmeter probe; and *P.El.*, pacing electrode. Arrows indicate direction of blood flow.

circuit. The brachiocephalic and left subclavian arteries were ligated just above the aortic arch, thus directing the cardiac output (excluding the coronary flow) into the extracorporeal circuit. An injection catheter was inserted into a femoral vein and connected to an infusion pump. A pacing electrode connected to a Grass stimulator (model S4) was sutured to the right atrium.

Aortic pressure was measured by a Statham P23Db transducer connected to a metal cannula which was inserted into the arch of the aorta. Left ventricular pressure was measured by a Statham P23Db transducer connected to a metal cannula inserted directly into the left ventricle. The first derivative of the left ventricular pressure curve, dp/dt, was obtained by an R-C circuit which continuously differentiated the pressure as measured by a Dallons-Telco micromanometer catheter. Aortic flow was metered by an electromagnetic flow probe placed either around the root of the aorta or in the extracorporeal circuit just beyond the Starling resistance. Heart rate was measured by a cardiotachometer. All values were

continuously recorded on a Sanborn direct writing recorder and intermittent high speed recordings were made on an Electronics for Medicine photographic recorder.

In each study the heart was paced at a rate just above the spontaneous rate. Next aortic flow and aortic pressure were set by adjusting the rotor pump and the Starling resistance. Following stabilization control recordings were taken. Then diphenylhydantoin 5 mg. per kilogram was administered intravenously over 2 to 3 minutes in nine dogs. A second injection of 5 mg. per kilogram of diphenylhydantoin was administered intravenously over 2 to 3 minutes to these same nine dogs 30 minutes after the first injection. Recordings were obtained a few seconds following the end of the injection. In five of those dogs, recordings were also obtained three, six and thirty minutes after the first and second injections. In four dogs (D-3, 6, 8, 9) 0.2 to 1.0 mg. per kilogram of propranolol was administered intravenously and bilateral midcervical section of the vagi was performed prior to the administration of diphenylhydantoin.

Measurements were made of aortic

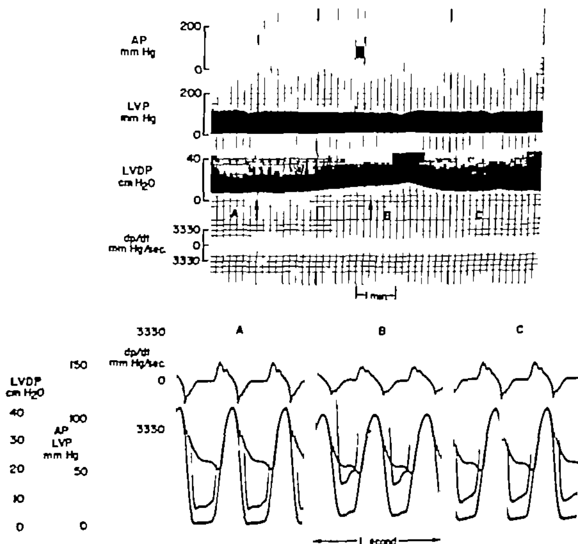


Fig. 2. Initial intravenous injection of 5 mg. per kilogram of Dilantin. *AP*, aortic pressure; *LVP*, left ventricular pressure; *LVDP*, left ventricular diastolic pressure; and *dp/dt*, rate of left ventricular pressure change. *A*, *B*, and *C* in upper low-speed tracing indicate times at which lower high-speed tracings *A*, *B*, and *C* were taken. First arrow indicates the beginning and second arrow the end of injection.

pressure aortic flow left ventricular pressure left ventricular end-diastolic pressure (LVEDP) and the maximal rate of rise of the left ventricular pressure (maximal dp/dt) Also stroke work (SW) stroke power (SP) and mean rate of ejection (MRE) were calculated[13] The performance of the left ventricle was evaluated by a method which has previously been described.[13] Changes in the maximal dp/dt SW SP and MRE of the left ventricle were related to the changes in LVEDP

First and second injections of quinidine gluconate as 5 mg per kilogram of quinidine base,* were given to six dogs the administration and experimental design were the same as for d phenylhydantoin In five of those dogs, recordings were taken at three six, and thirty minutes after the first and second injections. In three dogs (Q-3 5 6) propranolol administration and bilateral midcervical section of the vagi were carried out prior to the quinidine administration

The data were subjected to Student's t test for paired observations and independent samples. The level of significance was taken as $p < 0.05$

Results

Effects of Dilantin Typical recordings from an experiment (D 2) illustrating the effect of an initial 5 mg per kilogram injection of Dilantin administered over 2 to 3 minutes are shown in Fig 2 Following the injection of Dilantin LVEDP increased from 8 cm H_2O (control panel *A*) to 18 cm. H_2O (panel *B*) 30 seconds after the end of the injection while the maximal dp/dt decreased from 1,081 mm Hg per second to 779 mm Hg per second LVEDP and maximal dp/dt returned to near control levels within three minutes after the end of the first injection (panel *C*) A second injection of Dilantin administered 30 minutes after the initial injection resulted in a marked increase in LVEDP from a control of 10 cm. H_2O to 35 cm H_2O 10 seconds after the end of the injection while the maximal dp/dt decreased from 1 093 to 635 mm Hg per second At three minutes after the injection, there was still a marked effect present as the LVEDP was 41 cm H_2O and the maximal dp/dt was 947 mm Hg per second

A summary of the immediate effect of the first and second Dilantin injections upon the measurements and calculations used to evaluate left ventricular function is shown in Table I The most marked alterations usually occurred at this time. After the initial injection mean LVEDP increased and mean maximal dp/dt decreased Mean SW did not change significantly however mean SP and mean MRE decreased. Immediately following the second injection mean LVEDP increased and mean maximal dp/dt decreased more markedly than after the first injection. Also mean SW decreased and mean SP and mean MRE decreased more markedly The effect produced immediately after the second injection was significantly greater than that after the first injection It should also be noted that the results were similar in dogs with bilateral midcervical vagectomy and intravenous propranolol.

In order to evaluate the duration of the induced changes which followed the initial and second injections of Dilantin recordings were taken up to 30 minutes following the injections in five dogs (Table II) Immediately following the initial injection of Dilantin mean LVEDP increased and mean maximal dp/dt decreased. At three minutes after injection mean LVEDP was still above the control value but mean maximal dp/dt was not significantly different from the control level. At six and 30 minutes after injection mean LVEDP and mean maximal dp/dt were *not* significantly elevated Immediately following the second injection mean LVEDP increased and mean maximal dp/dt decreased more markedly than after the first injection. At three minutes after the injection, mean LVEDP was still above the control value and mean maximal dp/dt was still below the control level. At six and 30 minutes after the injection mean LVEDP and mean maximal dp/dt were not significantly different from control levels. The effects produced immediately after the second injection was significantly greater than that associated with the first injection. However the later effect of the second injection was *not*

*Quinidine base is 62.3 per cent of quinidine gluconate

Table I. Immediate effect of first and second Dil intin injection

Exp No.	Before: LVEDP (cm H2O)	Before: Max dp/dt (mm Hg/s)	Before: SW (g-m M)	Before: SI (cm M sec)	Before: MAP (sec)	After: LVEDP (cm H2O)	After: Max dp/dt (mm Hg/s)	After: SW (g-m M)	After: SP (g-m M)	After: MAP
First injection										
D 1	5	1 739	4 6	5	5 1	9	1 5 7	1 9	4 6	26 2
D [illegible]	8	1 091	8 0	55	6 6	19	[illegible]9	6 6	36 1	41 3
D 3†	5	1 740	6 2	13 1	36 4	9	1 433	5 5	36 5	5 1
D 4	1	0 3	7 9	50 0	43 0	1	1 794	6 9	37 3	35 7
D 5	5	2 463	5 3	41	36	8	1 810	4 5	35 0	39 9
D 6†	5	1 01	9 7	37 1	41 1	10	823	9 0	1[illegible]	40 3
D 7	11	2 155	13 6	78 6	69 9	18	1 784	13 1	7 1	66 9
D 8†	5	2 601	12 5	71 3	58 1	10	3 5	11 5	59 6	51 8
D 9†	8	2 [illegible]	10 9	71 7	59 9	13	1 841	1 1	73 8	63 4
Mean	7 4	1 895	8 7	55	47 8	13	1 573	8 3	47	43 4
SE	± 1 1	186	± 1 1	± 5 6	± 3 7	± 1 8	± 173	± 1 1	± 5 9	± 4 9
P value before and after first injection						< 0 001	< 0 001	< 0 2	< 0 01	< 0 05
Difference of means before and after first injection						+ 5 8	− 3	− 0 5	− 8 0	− 1 4
SE						± 1 0	± 49	± 0 3	± 1	± 1 5
Second injection										
D 1	3	1 822	2 8	15 3	16 5	[illegible]	1 577	2 6	13 5	15 5
D 2	10	1 093	9 2	63 4	56 6	35	635	6 9	35 0	41 1
D 3†	6	1 885	6 4	47 8	38 8	14	1 3 6	5 3	34 7	33 3
D 4	16	2 0 3	7 7	35 0	40 9	45	1 219	1	2 1	28 1
D 5	8	1 66	5 2	37 7	33 3	[illegible]0	880	1 0	24 1	24 1
D 6†	[illegible]	1 331	8 9	53 0	43 5	15	986	7 7	40 5	36 8
D 7	[illegible]	2 513	13 2	81 6	73 1	17	0 3	11 8	69 8	61 5
D 8†	8	2 570	13 0	71 4	59 3	15	2 130	12 1	62 1	52 8
D 9†	11	3 091	14 6	58 5	73 3	17	2 413	13 9	6 8	68 0
Mean	8 9	2 007	9 0	56 5	48 4	20 8	1 182	7 6	42 3	40 5
SE	± 1 3	± 306	± 1 3	± 7 8	± 6 3	± 3 9	± 200	± 1 4	± 7 5	± 6 0
P value before and after second injection						< 0 01	< 0 001	< 0 01	<0 001	< 0 001
Difference of means before and after second injection						+ 8 9	− 525	− 1 4	−14 5	− 9
SE						± 3 0	± 61	± 0 3	± 2 5	± 1 4
P value of difference of effect of first and second injection						< 0 02	< 0 01	< 0 01	<0 01	< 0 01

[illegible] LVEDP = left ventricular end-diastolic pressure; SW = stroke work; [illegible] = rate of injection.
[illegible] interval between injections [illegible] propranolol.

Table II Effect of first and second Dilantin injections followed for thirty minutes

Exp. No.	Control		Immediately after injection		3 minutes after injection		6 minutes after injection		30 minutes after injection	
	LVEDP (cm H_2O)	Max. dp/dt (mm. Hg/sec.)	LVEDP (cm H_2O)	Max. dp/dt (mm. Hg/sec.)	LVEDP (cm H_2O)	Max. dp/dt (mm. Hg/sec.)	LVEDP (cm H_2O)	Max. dp/dt (mm. Hg/sec.)	LVEDP (cm H_2O)	Max. dp/dt (mm. Hg/sec.)
First injection										
D-5	5	2 463	8	1 810	8	2 017	7	2 092	8	1 766
D-6	5	1 013	10	823	6	930	5	1 024	6	1 351
D-7	14	2 155	18	1 784	15	2 268	14	2 476	12	2 513
D-8	5	2 601	10	2 375	7	2 520	7	2 494	8	2 520
D-9	8	2 224	13	1 841	12	2 073	10	344	11	3 091
M	7 4	2 091	11 8	1 727	9 6	1 962	8 6	2 086	9 0	2 248
S.E.	± 1 7	± 281	± 1 7	± 251	± 1 7	± 273	± 1 6	± 275	± 1 1	± 308
P value of before and after first injection			< 0 001	< 0 02	< 0 02	< 0 3	< 0 1	> 0 9	< 0 20	< 0 60
Second injection										
D-5	8	1 766	20	980	14	1 282	13	1 3 0	11	1 188
D-6	6	1 351	15	966	10	1 200	8	1 345	7	1 681
D-7	12	2 513	17	2 023	15	2 180	12	2 450	13	2 180
D-8	8	2 520	15	2 130	10	2 400	9	2 344	9	2 513
D-9*	11	3 091	17	2 413	15	2 652	12	2 947	11	3 151
Mean	9 0	2 248	16 8	1 706	12 8	1 913	10 8	2 091	10 2	2 144
S.E.	± 1 1	± 308	± 0 9	± 302	± 1 2	± 296	± 1 0	± 316	± 1 0	± 338
P value of before and after second injection			< 0 01	< 0 01	< 0 01	< 0 02	< 0 02	< 0 1	< 0 10	< 0 60

*Bilateral [illegible]

significantly different from that associated with the initial injection

The development of pulsus alternans following an initial 5 mg per kilogram injection of Dilantin was seen in two dogs (not included in Table I) The death of one animal occurred following an initial injection of 10 mg per kilogram of Dilantin intravenously over three minutes This was never seen with an initial 5 mg per kilogram dose but was seen occasionally following a third or fourth 5 mg per kilogram injection given at 30 minute intervals Ventricular fibrillation did not occur in any of the experiments following Dilantin administration

Control injections with the diluent alone were performed in six experiments in three dogs Injection of this material was without significant effect on the performance of the left ventricle

Effect of quinidine Typical recordings from an experiment (Q-3) illustrating the effect of an initial 5 mg per kilogram injection of quinidine base administered over 2 to 3 minutes are shown in Fig 3 Following the initial injection of quinidine the LVEDP increased from 6 cm H_2O (control panel *A*) to 9 cm H_2O (panel *B*) ten seconds after the end of injection while the maximal dp dt decreased from 2 023 to 1 445 mm Hg per second Three minutes after the end of the injection the LVEDP was 8 cm H_2O and the maximal dp/dt was 1 565 mm Hg per second (panel *C*) The second injection of quinidine administered 30 minutes after the initial injection resulted in an increase in LVEDP from to 12 cm H_2O 10 seconds after the end of the injection while the maximal dp dt decreased from 1 753 to 1 275 mm. Hg per second Three minutes after the injection the LVEDP was 11 cm H_2O and the maximal dp dt was 1,332 mm Hg per second

A summary of the immediate effect of the first and second quinidine injections upon the measurements and calculations used to evaluate left ventricular function is shown in Table III Immediately following the initial injection mean LVEDP increased while mean maximal dp/dt decreased Mean SW mean SP and mean MRE all decreased Immediately following the second injection the increase in mean LVEDP and the decrease in mean maximal dp dt were similar to after the first injection Mean SW mean SP and the mean MRE all decreased The immediate effect following the second injection was not significantly different from that measured following the first injection. It should be noted that the results were similar in

*[illegible] of diluent 40 per cent propylene glycol and 10 per cent [illegible] water [illegible] pH adjusted with NaOH to 11 1

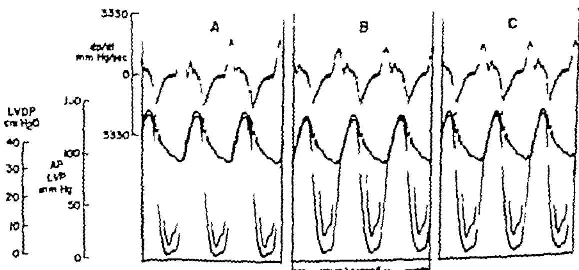


Fig 3 Initial intravenous injection of 5 mg per kilogram of quinidine base Symbols as in Fig 2 *A* Control tracing *B* tracing 10 seconds after quinidine injection *C*, 3 minutes after quinidine injection

Table III. Immediate effect of first and second quinidine injections

Exp. No.	Before: LVEDP (cm H_2O)	Before: Max dp/dt (mm Hg/sec)	Before: SW (Gm. M)	Before: SP (Gm. M/sec)	Before: MRE (/sec)	After: LVEDP (cm H_2O)	After: Max dp/dt (mm Hg/sec)	After: SW (Gm. M)	After: SP (Gm. M/sec)	After: MRE (/sec)
First injection										
Q-1	5	1 822	5.2	35.6	39.5	8	1 596	5.2	40.3	36.4
Q-2	8	1 904	9.8	49.0	42.5	11	1 341	8.4	40.0	36.2
Q-3	6	2 023	10.0	69.0	54.5	9	1 445	8.8	62.0	51.4
Q-4	7	1 445	10.3	51.5	43.5	12	986	9.1	41.9	38.2
Q-5	7	413	11.1	70.7	52.9	10	1 627	10.1	64.2	49.1
Q-6	7	2 400	10.1	67.8	51	10	1 979	9.9	60.0	47.3
Mean	6.7	2 001	9.4	58.9	47.4	10.0	1 579	8.6	51.4	43.1
S.E.	± 0.4	± 151	± 0.9	± 4.7	± 2.6	± 0.6	± 142	± 0.7	± 4.8	± 2.8
P value of before and after first injection						< 0.001	< 0.01	< 0.02	< 0.001	< 0.001
Difference of means before and after first injection						+ 3.3	− 422	− 0.8	− 7.5	− 4.3
S.E.						± 0.3	± 104	± 0.2	± 0.7	± 0.5
Second injection										
Q-1	7	2 023	5.2	46.0	39.8	10	1 627	5.0	4 0	37.8
Q-2	11	1 571	8.4	30.3	35.5	17	1 232	7.5	30.9	29.6
Q-3	7	1 753	8.3	53.0	46.4	12	1 275	6.6	42.3	38.5
Q-4	9	1 395	11.4	58.2	46.4	13	993	10.1	47.0	39.5
Q-5	7	1 557	11.2	75.2	55.0	11	1 646	10.6	67.9	51.3
Q-6	9	1 885	9.5	66	53.4	12	1 646	9.0	57.0	46.8
Mean	8.3	1 864	9.1	56.7	46.1	12.5	1 403	8.1	47.9	40.6
S.E.	± 0.7	± 166	± 0.9	± 5.3	± 3.1	± 1.0	± 113	± 0.9	± 5.3	± 3.1
P value of before and after second injection						< 0.001	< 0.01	< 0.01	< 0.001	< 0.01
Difference of means before and after second injection						+ 4.2	− 461	− 0.9	− 8.8	− 5.5
S.E.						± 0.5	± 96	± 0.2	± 1.2	± 0.9
P value of difference of effect of first and second injections						< 0.3	< 0.7	< 0.7	< 0.3	< 0.3

Bilateral midcervical ag my and intra enous propranolol

Table IV Effect of first and second quinidine injection followed for thirty minutes

Exp	Control LVEDP (cm H_2O)	Control M dp/dt (mm Hg/sec)	Immediately after injection LVEDP (cm H_2O)	Immediately after injection M x dp/dt (mm Hg/sec)	3 min after injection LVEDP (cm H_2O)	3 min after injection M x dp/dt (mm Hg/sec)	? min after injection LVEDP (cm H_2O)	? min after injection M dp/dt (mm Hg/sec)	30 min after injection LVEDP (cm H_2O)	30 min after injection M dp/dt (mm Hg/sec)
First injection										
Q	8	1 901	11	1 841	10	1 821	1	1 747	11	1 571
Q 3	[illegible]	2 021	9	1 445	8	1 565	7	1 734	7	1 751
Q 2	7	1 445	12	986	10	1 200	9	1 761	[illegible]	1 395
Q 5	7	2 413	10	1 627	9	1 885	8	073	7	557
Q 6	7	2 400	10	1 979	8	2 023	8	2 073	8	2 491
M	7 0	017	10 4	1 376	9 0	1 699	8 8	1 7 8	8 4	1 954
SE	± 0 3	± 179	± 0 5	± 173	± 0 4	± 145	± 0 9	± 149	± 0 7	± 240
P (compared with control after first injection)			< 0 01	< 0 0	< 0 01	< 0 02	< 0 05	< 0 01	< 0 10	< 0 50
Second injection										
Q	11	1 571	17	1 232	16	1 370	15	1 516	13	1 973
Q 3	7	1 751	1	1 75	11	1 332	9	1 451	7	1 784
Q 4	[illegible]	1 395	13	993	12	1 018	1	1 06	12	1 175
Q 5	7	2 557	11	1 646	10	1 811	[illegible]	1 915	9	2 190
Q 6	9	1 885	1	1 646	11	1 766	11	1 901	7	2 155
M	8 6	1 931	13 0	1 458	1 0	1 465	11 2	1 880	9 6	1 857
SE	± 0	± 199	± 1 0	± 127	± 1 0	± 131	± 1 1	± 161	± 1 2	± 180
P (compared with control after second injection)			< 0 001	< 0 0	< 0 01	< 0 05	< 0 01	< 0 1	< 0 40	< 0 [illegible]

[illegible] A + B [illegible]

described t as surprisingly similar to that reported by Scher and Young[1] in dogs. This activation sequence in dogs has been duplicated in detail by us in our laboratory. The duration of the ventricular depolarization was assumed to be 80 msec. The physical orientation of the heart was chosen from standard cross-section anatomy of the heart and correlated with normal chest roentgenograms.

The heart was pictured as consisting of 20 segments of myocardium: 7 of approximately equal size represented the septum, 9 of approximatel equal size represented the left ventricle, and 4 of approximately equal size represented the right ventricle. Each of the 20 current dipoles was placed at the centroid of the segment of myocardium that it epresented. Coordinates of these points were determined and direction cosines for each of these dipoles were assigned so that the dipole vector was normal to the mean wave front as it advanced from endocardium to epicardium through the myocardium. The dipole locations and direction cosines assigned for the 20 current dipoles are shown in Table I.

As the advancing wave f ont of depolarization passes th ough any given segment it is assumed to be a dipole layer as described by Craib. The left ventricular myocardium was assumed to be activated from endocardium to epicardium with no activation assumed to be in the reverse direction. The septum was assumed to be activated 80 per cent left to right and 20 per cent right to left. The right ventricle was assumed to be activated from endocardium to epicardium throughout. The time history of dipole moment strength of any given segment of left ventricular myocardium for example would then have an onset time when the wave front entered that segment carried there by the Purkinje fibers along the inner surface, a time when the wave front fills the segment and an offset time when the wave front exits from the block.

An examination of the experimentally determined dipole moment function is seen in Fig 1. Twenty multipoint Scher needles, consisting of 15 intramyocardial electrodes spaced at 1 5 mm intervals along a central shaft with the entire needle less than 0 03 mm in diameter

Table I Tabulation of the location and direction cosines of each of the 20 dipoles

D pol	Location			Direction cosine		
		y		l	m	
1	12 3000	4 0000	13 7000	−0 1600	0 2500	0 9550
2	13 4000	3 0000	15 5000	0 5700	−0 2500	0 7800
3	13 0000	6 0000	13 5000	0 3300	0 5400	0 7700
4	11 6000	2 0000	13 8000	−0 2900	−0 5600	0 7800
5	11 7000	6 9000	11 9000	−0 2100	0 7400	0 6400
6	9 9000	2 8000	12 5000	−0 8400	−0 2800	0 4700
7	10 7000	4 8000	12 7000	−0 7100	0 3400	0 6200
8	14 8000	3 5000	13 7000	0 7800	−0 5000	−0 3800
9	15 3000	3 5000	14 3000	0 9800	0 1500	−0 1000
10	13 6000	1 7000	14 0000	0 3200	−0 9300	0 1800
11	14 2000	4 5000	11 4000	0 4500	−0 3500	−0 8200
12	14 1000	7 5000	12 6000	0 6800	0 7200	−0 1400
13	11 8000	1 9000	12 4000	−0 3700	−0 9200	−0 1300
14	12 6000	5 0000	9 8000	0 0300	0 0300	−0 9990
15	13 0000	7 7000	10 9000	0 2100	0 9400	−0 2800
16	10 5000	3000	10 8000	−0 7100	−0 6500	−0 2700
17	11 5000	2 0000	16 0000	0 3600	−0 6100	0 7100
18	8 8000	2 5000	14 8000	−0 7100	−0 5900	0 4000
19	10 5000	8 2000	14 5000	−0 5200	0 5200	0 6800
20	10 9000	5 9000	15 5000	0 3300	.00	0 8200

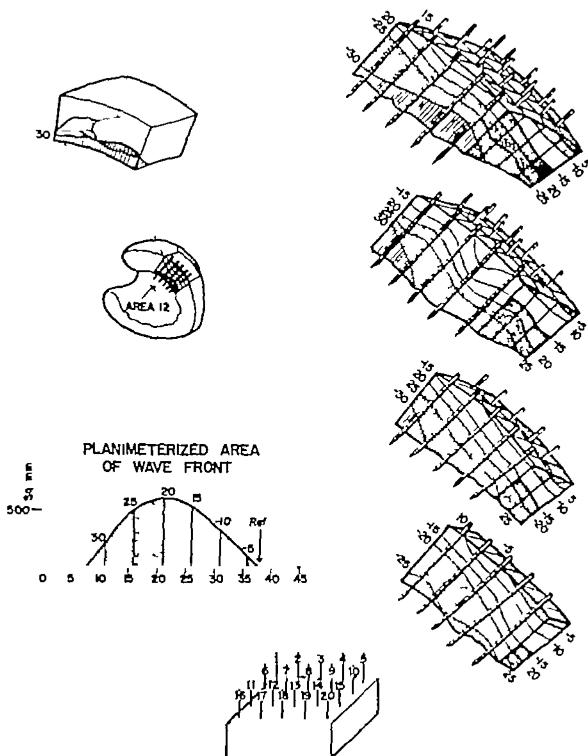


Fig. 1. Detailed sequence map of segment 1... There are 20 multipol t lectrodes i serted in gral of 4 row with 5 needles each. The needles ar 5 mm part. The area of the w front it p ses th ugh the segment is shown in the diagram t the lower left.

were placed in a local area of myocardium for a detailed examination of this area. These 20 needles were placed in 5 rows of 4 each with each needle 5 mm from its neighbor on a grid measuring 2 by 1.5 cm. The segment illustrated approximates segment 12 of the model. The myocardium was mapped in detail. A three-dimensional diagram was constructed of a wave front as it passed through the segment and the area of that wave front at each 5 msec. was measured. This was done by cutting the segment into 5 mm. slices, measuring the actual length of the wave front on each surface of each slice, and constructing a trapezoid with these measurements from which the area could be readily approximated. The area at any one point in time was the sum of all such trapezoidal segments seen in each of the 3 slices examined in such detail. The area of the advancing wave front in this block is a function of time, as seen in this diagram. If one assumed a uniform distribution of current dipoles over this surface, then the dipole moment strength would be proportional and would have the same functional form.

Since the activation wave front enters any block of myocardium somewhat obliquely because of the rapid Purkinje spread to the endocardium as compared to the slower propagation throughout the myocardium, the actual area of the dipole layer will increase gradually until it has its maximum area. It will then pass through the block at approximately uniform strength until some area of this wave front exists from the block, at which time there will be a decay of current strength as the wave front continues to progress out of the block. In the model reported here, these 4 points in time were represented by 4 constants called K1, K2, K3, and K4. K1 is the onset time, K2 the time at which the maximum current moment occurred and the wave front has its maximum area, K3 the time when the moment began to decay because the wave front began to disappear from the block, and K4 the time at which the dipole layer exited from the block entirely. A maximum value (K max) was assigned to each left ventricular segment. Since each left ventricular segment was chosen to be of the same size, the K max was the same in all 9 left ventricular segments and was proportional to the area of the wave front as it filled that segment. To make a rounded curve a cosine function was assigned between K1 and K2, a straight line was assigned between K2 and K3, and a cosine function again assigned between K3 and K4 (Fig. 2). Since the septum was assumed to be 80 per cent depolarized left to right and 20 per cent right to left, one fourth of the left-to-right activation would be cancelled out so the total amplitude of the dipole moment from any block of septal myocardium would be approximately 60 per cent of what it would have been had the activation been entirely in one direction. The time histories and magnitudes of the dipole moment strength used in this model are summarized in Table II.

This set of current dipoles was placed

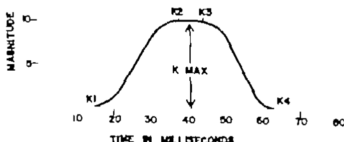


Fig. 2. A typical dipole time history (here segment 12) is shown. *K1* is the onset time. *K2* is the time that the advancing wave front fills any given segment, *K3* is the time the wave front begins to leave that segment, and *K4* is the exit time when the front leaves the segment altogether. *K MAX* is the magnitude at the peak and is proportional to the area of the wave front as it fills the segment.

Table II. K1 is the time of onset of a given dipole, K2 is the time it reaches peak value, K3 is the time it begins to decay in strength, and K4 is the offset time. K max is the relative strength of each dipole moment

Dipole	K1	K2	K3	K4	K max
1	−5	15	16	32	4 0000
2	8	28	30	50	3 0000
3	6	26	28	48	3 0000
4	12	35	37	57	3 0000
5	16	24	48	68	5000
6	25	35	70	82	2 5000
7	30	50	64	82	2 5000
8	13	32	46	58	10 0000
9	14	35	45	62	10 0000
10	15	34	42	55	10 0000
11	7	38	55	68	10 0000
12	19	36	54	72	10 0000
13	20	34	43	55	10 0000
14	18	55	67	82	10 0000
15	28	50	65	80	10 0000
16	33	52	58	4	10 0000
17	13	28	30	45	3 5000
18	31	50	52	62	4 5000
19	35	53	55	80	4 5000
20	33	48	55	70	4 5000

in a uniform resistive medium and 4 observers were stationed in the medium at appropriate distances away from this simulated heart to represent a Cube system electrode placement on a normal male thorax, and a sphere was passed through these 4 points. Thus the model is a system of dipoles representing the heart eccentrically located in a homogeneous resistive sphere with 4 pickup electrodes on the surface on axes orthogonal to each other to represent a Cube system electrode placement. The behavior of this system is governed by the equation of Wilson and Bayley. This is model 3 of Appendix A. In this simulation the medium inside the sphere had finite resistivity and the medium exterior to the sphere had infinite resistivity. The internal tissue inhomogeneities were ignored and the only electrical activity considered was ventricular depolarization (QRS). The present model does not include atrial depolarization (P) or repolarization (Ta) or ventricular repolarization (ST and T).

Simulated normal vectorcardiograms. When all 20 dipoles are given their time histories according to the activation sequence described above and the sum computed over time to the 4 body surface points, then by proper combination of X, Y and Z orthogonal components a horizontal, frontal and right sagittal vectorcardiogram can be generated (Fig 3).

Simulated left and right ventricular hypertrophy. Hypertrophy of the left ventricular segments was simulated by increasing the duration of each of the left ventricular segments to simulate thickening of the ventricular wall. In the examples shown in Fig 3 the duration of all left ventricular segments was increased by a factor of 1.57. In both of these simulations the onset time was assumed to be unchanged, i.e. the conduction to the inner layers was assumed to be normal.

Dilatation of the left ventricle was simulated by increasing the current moment of these segments to correspond to an increase in the over all area of the depolarization wave front within any given segment and the dipole location for each of these were moved outward and downward. In the simulation reported here the current moments were increased by a factor of 5. In a similar manner right ventricular hyper

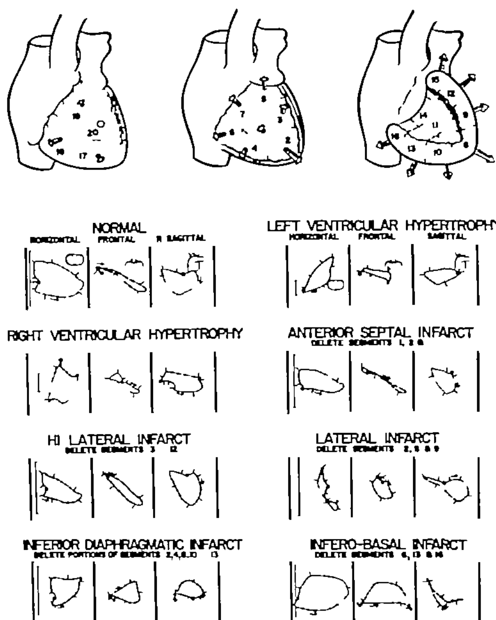


Fig 3 Simulated basic l ectrocardiograms Righ and lef entricular hypertrophy ere simulated by increasing the duration nd magnitude of the segments representing the respectiv entricle Enlargement was simulated by moving he location of each dipole out t correspond th the degree of enlargemen Typical large infarcts are simulated by inactiv ting several segments t time These simulated ectrocardiogr m resemble those seen in li al ectrocardiograph

tropl y was si lated l y ncreasing the duration and the m gn tud of the right entricula segment

Simul ted l rge inf ct The large classi cal nfarcts n the usual location shown n Fig 3 were si ulated l removing several seg ent for x pl th se n the tero-septal region were removed to simulate large nteroseptal myocardial infarction To do this the magnitude of these several segment was reduced to zero and the problem omputed as befor

S m l ted moderat sized myoc rdi l n farct Moderate-si ed nfarct ons were

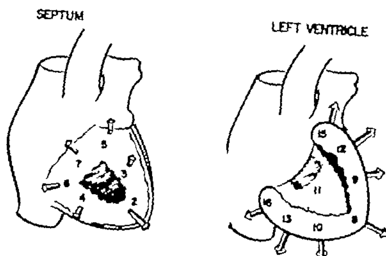


Fig 4 M d t -sized nfar ts are simul ted th the model by inactivating one segment t 1 t me for each of these 7 sept l nd 9 left ventricular segments

si ul ited l y removing one segment at a t i e fr m each of eptal segments and ventricular segments i.e the magnitude of one segment at a time was reduced to zer (Fig 4) The vectorcardiographic loops resulting f om each of these reduc tions are recorded in Fig 5

Simulated small infa cts Infarcts repre senting about 1 c c of myocardium were simulated l y introducing an additional u rent dipole function wh ch had a nega t e amplitude that was less in magnitude and less n duration than the segment n qu stion l ut placed at the same loca t on and g ven the same direction cosines. In effect these ? current dipoles were then seen as one and the sum of the two repre sents the g ven function that would repre sent thi a ea (F gs 6 and) In th s imulat on a magnitude of −4 5 was used with a duration of msec so the area represented by the negative function of any left ventricular curve is approximately 10 per cent of the total area of that curve Thus this simulation would represent an infarction of approximately one tenth of the mass of any given segment of myocardium or somewhat less than 1 per cent of the total cardiac mas

Results

It will be noted that the simulated normal vectorcardiogram does indeed re semble the normal ones seen in the Cube system of electrode placement With the model a single equivalent d pole wa formed by coalescing all the dipoles to the centroid of the heart This, then produced an equivalent dipole It is of interest to note that when this was done there was an increase in the AI dimension and the resultant vectorcardiographic loop re sembled a corrected lead system Th e greatest change occurred in the horizontal and sagittal plane vectorcardiograpl ic loops. The frontal plane loops were r tl er insignificantly different

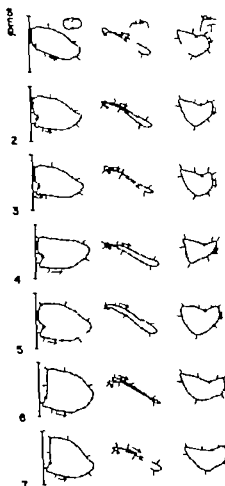
Simulated left ventricular hypertrophy produced a marked increase in voltage towards the left ventricle and a loop which does indeed resemble actual left ven tricular hypertrophy Simulated right ven tricular hypertrophy likewise produced marked displacement of the middle and late QRS vectors anteriorly and inferiorly this of course is routinely seen in moder ately severe and severe right ventricular hypertrophy in the Cube system of elec trode placement

A review of tl e vectorcardiogram of simulated large infarcts in all the classical locations showed a rather remarkable resemblance between them and ones re corded in clinical vectorcardiogr u l s f large infarcts in these same location When moderate-sized infarctions were simulated by decreasing the magnitude of one seg ment at a time to zero in each of 16 d pole locations (Figs. 4 and 5) both familiar and unfamiliar patterns evolved It worth noting at thi point h wever tl at tl e rem n d f t y ne f tl e 1(l j les

SIMULATED - NORMAL



SIMULATED MODERATE SIZED SEPTAL INFARCTS



MODERATE LV INFARCTS

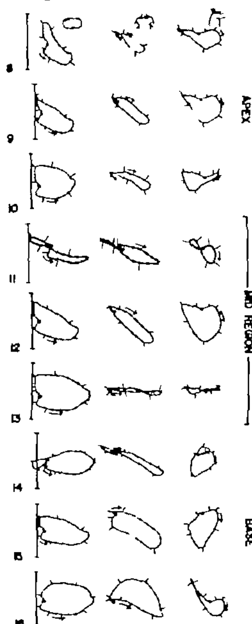


Fig. 5. Here is presented atalogue of simulated moderate-sized infarcts throughout the septum and left entricle in the apex, midregion and base. The number t the left of each vectorcardiogram represents the segment deleted. Some of these are familiar patterns in clinical vectorcardiography others less familiar. When the control record is ilable f r omparison, however infarction simulated anywhere in the sept m or left entricle produces defin hange.

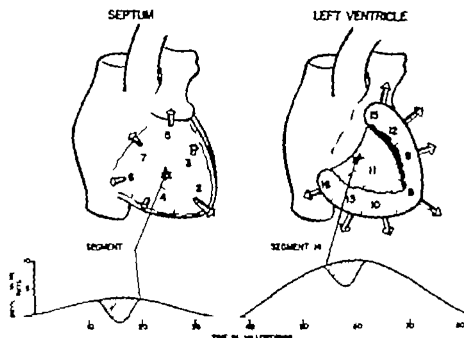


Fig. 4. Sc ll nf n s lated a of the 16 d pole k tion b pro ng s ll seg t f m m t he me h t m l giving t the e lirection The prog m sees the 2 dipoles one here depict l the hed l ne below the haded The l me of he rt represented by the shaded re is pproximat l 10 p t of ach lef entric l r segme t nd 15 p t of each sept l seg ment with he l ft h el he left h ll at he sep

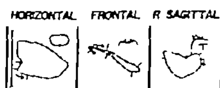
used nth nt el ange in resultant potential held as measured at the surface when compared to a control record. When septal segment were removed especially the l s l septal segments there was m more se n the posterior components, and loops resembling left ventricular hyper trophy w re seen. When apic l segments of the left ventricle e segment 8 or 9 were removed and espe ially when both wer ren oved it one t me pattern re sembling peri inf rction blo k were produced without ntroducing del y in the program t any portion f the heart.

When segments of the true posterior wall of the left ventricle i e segment 11 and 14 were ren ved patterns resembling incomplete right bundle branch block or right entricul r hypertrophy were seen. Here a in these pattern resembling conduction l l were observed without intr lu ing l l y to ny segment of the computer program. When superior and basal segment were removed there was a hift of the l t vert or right var l and inferior wit a hift f the mean ax m l w l. When b t r ic t l s of

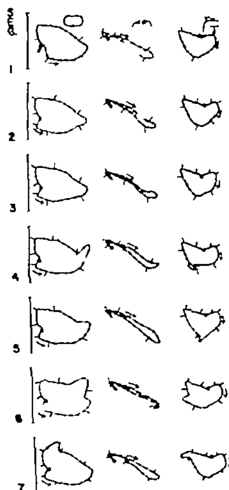
segments were removed there was a definite left axis deviation of the late QRS vector resembling the parietal block of Grant with a shift of the mean axis toward the left. Here again the delay was not introduced into the computer progr suggesting that these pattern termed conduction delay such as incomplet right bundle branch block, pariet l block, and peri infarction block, may be at tim s only the result of a loss of myocardium without conduction disturban es.

While sm ll infarct were simulated representing the loss of approximately 10 to 15 per cent of any one f th sept l or 9 left ventricular segment it w noted th t ther were no truly silent area in the myocardium and that a 10 per cent loss of any left ventricular segment or a 15 per cent los f any sept l segment w readily seen t l hu t l inge t the vect rcardiograph l ops small ted. A catalo ue of th el nges l th with n t sized infarct and these small infarct mulated in each of the 7 sept l segment nd 9 left ventricul r seg t p sented n th paper n th l g th t n

SIMULATED - NORMAL



SIMULATED SMALL SEPTAL INFARCTS



SMALL LV INFARCTS

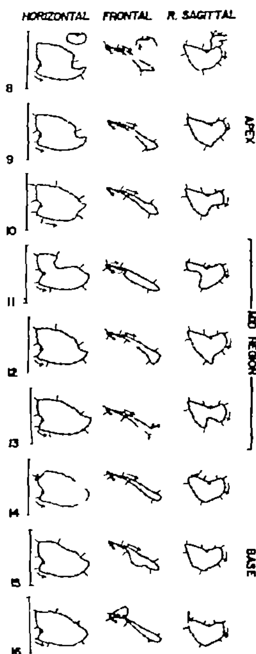


Fig. 7. Presented here are simulated small infarcts involving approximately 15 per cent of the volume of each septal segment (located on the left half of the septum) and approximately 10 per cent of each left ventricular segment. The number to the left of each vectorcardiogram represents the segment in which the small infarct was located.

will stimulate a search for many of these patterns in clinical vectorcardiographic material with autopsy confirmation

Discussion

In the evaluation of the basic assumptions that go into this model it should be made clear that the physical location and anatomical orientation of the various segments of the heart were based on textbook anatomy and confirmed by observations of normal human chest x rays and autopsy findings. The sequence of human ventricular depolarization was assumed to be similar to that in dogs. This assumption needs to be experimentally validated in more detail. Scher and Young, Hamlin and Hamlin and Scher have shown considerable variation among various animal species, and it would not be surprising if considerable variation is to be found between the dog and the human being. On the other hand several lines of indirect evidence can be brought to bear on the assumption that the dog's sequence of activation is indeed similar to that of man. Much of the progress that has been made in human electrocardiography and vectorcardiography is based on experimental lesions and conduction abnormalities produced in dogs over the last several years. An extrapolation to human beings has been done with some considerable success. Recently Durrer and associates[10,1] have demonstrated in revived perfused human hearts and in a limited number of explorations in intact human beings, that the activation of the free left ventricular wall near the septum and the free right ventricular wall is what would be expected in extrapolating Scher's activation sequence to the human being. More recently Durrer and his group reported extensive studies that used a perfused human heart which was kept viable for a long period of time and activated through the conduction system by stimulating the atria. It was observed that the human activation sequence was surprisingly similar to that seen in the dog.

The functional form which would represent any given segment of myocardium was examined by us in a number of segments of the left ventricle in considerably more detail than it had been in any of our previous experiments or in those reported by Scher. The inner portion tended to be activated more rapidly than the outer portion (Fig 1) however except for areas immediately adjacent to the large anterior papillary muscle there was never any deep Purkinje penetration into the wall with propagation towards the endocardium. In every case the propagation was activated routinely from endocardium to epicardium with the inner third activated more rapidly than the outer third. Examination of the curve representing the area of that wave front within any given segment as seen in Fig 2 reveals a functional form quite similar to that used in this model except that the rising slope of this curve is somewhat more rapid than usually used in this model while the decaying slope is approximately the same. A study to measure the magnitude of the dipole moment strength in the inner third as compared to the middle third and outer third is underway in this laboratory. The actual wave form of the intramyocardial needles was observed and averaged over a number of these needles. Preliminary examination of these data suggests that the inner third carries a smaller magnitude than the outer third but exhibits the same general wave form. This decrease in magnitude would tend to decrease the amplitude used in the model to represent the inner portion of the myocardium as compared to the outer portion and would tend to return the rising slope of this curve more nearly to that actually used in the model. These observations need to be examined in more detail before any final comment on this can be made.

Prinzmetal and his co-workers[11] have argued for a number of years that the inner third of the myocardium is silent producing no effective voltages that can be measured at the surface. On the basis of clinical and experimental data, Sodi Pallares and Calder[1] and others[1] have hypothesized that the base of the septum and left ventricle as well as the inner one half to two thirds is silent and have assumed that destructive lesions in these areas would produce no significant change in the surface electrocardiogram. Scher and Young[1] have argued from their intramyocardial maps (and we concur [illegible] on

the basis of the detailed intramyocardial maps and intramyocardial wave forms and voltages) that the inner third while contributing less to the total over-all voltage than the outer third of the ventricular wall can by no means be considered to be electrically silent Experimentation with our model which is based on carefully constructed activation sequences, supports these conclusions. In the model small infarcts in any of these locations produced discernible changes in the vectorcardiographic loops simulated It should be noted however that infarction of the basilar portions of the left ventricular wall produced abnormalities in the terminal portions of the QRS loop If one is limited to the traditional notion of clinical electrocardiography that the diagnosis of myocardial infarction is made from abnormalities in only the first 0 04 second of the QRS then of course one would be unable to diagnose such lesions.

In our analogue simulation of the vector cardiogram a normal loop was generated when the activation sequence was assumed to be similar to that in dogs. Furthermore, varying degrees of right ventricular hypertrophy left ventricular hypertrophy large infarcts, and conduction defects could be readily simulated if the activation sequence were the same. These simulations also support the validity of the sequence They would also suggest that the tissue inhomogeneities, including the external boundary and distance effects from various portions of the heart to the surface electrodes, do not play a major role in most persons, at least when vectorcardiograms are recorded

This digital simulation was undertaken to evaluate the order of magnitude of distance and boundary effects. In the first effort not described here in detail (Model 2 of Appendix A) distance effects were recorded between this distributed set of 20 dipoles and observer electrodes stationed in an infinite homogeneous resistive medium so as to represent the Cube system of electrode placement on a phantom thorax. It was observed that this system was particularly sensitive to basal portions of the septum sensitive in general to the right ventricle and less sensitive to segments from the left ventricle The placement in this infinite homogeneous medium of a spherical boundary passing through these same observer points effected the result only moderately and made the distance effects less noticeable i.e. the resultant loops were somewhat more like the infinite dipole model Brody [7] Nelson and his associates and others[8-10] have demonstrated both theoretically and experimentally that the intracardiac blood mass, which is an important inhomogeneity tends to emphasize the dipole equivalent When these inhomogeneities are included in the simulation the spherical model would be expected to become more like the infinite model

These data reveal one of the more significant reasons for developing a mathematical model of the electrical fields of the heart and simulating a vectorcardiogram Once a reasonably good model of the cardiac generator and its volume conductor is accomplished a large number of experiments can be run by simply changing a few input cards of the computer program. In a few hours (and a few minutes of computer time) data can be accumulted for a large number of experiments. Years of time would be consumed in the accumulation of an equivalent amount of data with traditional methods. The experimentor would have to observe clinical patients wait for these lesions to develop catalogue them and then relate them to autopsy findings. The computer simulation pinpoints areas of experimentation and clinical observation that are more likely to yield significant results and of course all such simulations must be clearly validated clinically before their significance can be assessed properly

An illustration of the use of the model to pinpoint significant clinical correlations and possible experiments, was recently reported by us. In this investigation with the model the effect of lesions of various sizes on the surface vectorcardiogram was studied. An attempt was made to determine the smallest lesion which would produce significant vectorcardiographic changes above anticipated noise levels. The model clearly suggested that lesions 0.3 by 0 6 by 0 6 cm in the heart would produce changes on the surface vectorcardiogram no matter where they were located and that these could be seen if

a previous control record without such lesions were available for comparison.

This model then clearly suggests that pathologic examinations of the heart must be detailed if one is to ascertain to what degree living hearts follow this model. To test this hypothesis, serial sections of the entire heart are needed at intervals of 5 mm. or less, as done by Ehrlich and Schinohara[22] at the Bronx Lebanon Hospital in New York. Microscopic studies and special stains of the entire heart would need to be done at this interval because as they observed many of these small lesions are not visible grossly. Furthermore, in order to avoid such laborious microscopic sectioning of the entire heart and to more easily identify these small lesions, a stain which could be applied grossly is needed, such as nitro blue tetrazolium chloride (suggested by Nachlas and Schnitka[23]). Detailed mapping of destructive lesions of the myocardium needs to be correlated both with a detailed study of vectorcardiograms with various lead systems and also with conventional 12 lead electrocardiograms taken on high frequency recording instruments to determine to what degree these tiny "bite-out" lesions, as seen in the vectorcardiographic loops, can be correlated with small areas of pathology scattered throughout the myocardium.

It is a well known clinical observation that gross changes in the volume conductor such as severe obesity, pleural effusion, pericardial effusion, emphysema, pneumothorax, and gross chest deformity may drastically alter the potentials as seen on the surface. Clearly, a further exploration of this model with a more realistic volume conductor than the homogeneous sphere with eccentric dipoles is needed. Work has been in progress in our laboratory using the Gelernter-Swihart[12] approach to simulate a realistically shaped male torso with realistically shaped internal inhomogeneities. Initial data from this model with a homogeneous torso were recently reported[24] and transfer numbers or transfer impedances from a current dipole of unit strength in the heart to the total body surface have been generated for each of the 20 dipoles in this model. Then with the use of our generator model and by superposition it was possible to simulate a normal total body surface ECG. It was noted that this total body surface ECG did indeed resemble that recorded by Taccardi[25] in a normal male chest. Since this model generates a total body surface electrocardiogram, any lead system may be picked up from the surface and simulated. Each lead system can be tested to determine which lead system tracks most closely the lesion seen in the simulated heart, which is, of course, entirely specified. If none of these lead systems record the changes adequately, then by optimizing techniques the surface map can be explored with a computer program for alternate lead systems that would be more adequate in depicting the lesion simulated.

Our experimentation with this model to date reaffirms our initial impression that a model such as this, which is physiologically and anatomically based and which takes into account the actual location of the cardiac generators within the myocardium, does yield surface vectorcardiograms which can be used to derive the parameters of this set of simulated cardiac generators. It seems clear at this point that such a model is more capable of rational interpretation than such empiric constructions as the single fixed-locus dipole with a multipolar expansion at the same location as proposed by Geselowitz and co-workers,[26] and others.[27,28] This latter approach can be related to physiology and anatomy only in some empirical and indirect way.

Summary and conclusions

1. Experiments with a mathematical model of the electric field of the heart where the 20 current dipoles are eccentrically placed in a spherical medium of uniform resistivity and observers are placed on the surface of this sphere to represent a Cube system of electrode placement are reported.

2. In the simulated Cube vectorcardiogram, a normal vectorcardiogram was simulated, as were varying degrees of right and left ventricular hypertrophy and large myocardial infarction in the classical locations.

3. All areas of the heart were methodically explored and medium and small

infarcts were simulated in the 16 locations of the septum and left ventricle and catalogues of these findings are presented

4 Special attention was paid to the so-called silent areas, i.e. basilar portions of the septum and left ventricle and the inner half of the left ventricle. Small lesions in any of these locations produced clearly discernible changes in the simulated vectorcardiogram

5 Attention is called to the serious need to improve pathologic scanning of the myocardium for these small lesions in order to further validate the clinical significance of these observations.

6 Further exploration of a more realistic simulation of the irregularly shaped human torso with the internal nhomogeneities, such as lungs, fat intracardiac blood mass, large vessel blood masses, etc is clearly indicated

7 As work progresses in this model it becomes increasingly clear that a model such as this, which is physiologically and anatomically based can be expected to remove a considerable amount of the empiricism that has undergirded the electrocardiographic and vectorcardiographic fields. Such a model will also place the study in these specific fields on a more rational physiologic basis.

Computations in these simulations were done on an IBM 7094 All-purpose Computer at the Health Sciences Computer Facility University of California t Los Angeles

Appendix A

Mathematical models of the electrical activity of the heart

Three models of the heart were studied Basically all three consisted of an N dipole heart imbedded in a medium The amplitudes of the dipoles varied with time but their orientations were kept fixed Four observer electrodes were placed at certain locations. Three electrodes determined the Cartesian coordinate system and the fourth was the reference Measurements of potential are given relative to this fourth observer The well known dipole formula

$$V = \frac{F \cos\theta}{r^2} \qquad (1)$$

will be the point of departure for the three models. These models will be described in order of increasing sophistication

In Model 1 we considered a homogeneous medium of infinite extent in which were imbedded N dipoles. The electrodes were assumed to be far enough away to make the heart appear as a point Three of the electrodes were placed on the coordinate axes x y and z often denoted in mathematical context by the subscripts j = 1 2 3 in that order The fourth reference observer was assumed to be infinitely distant and hence exerted no potential there. For simplicity we placed the N dipoles (the heart) at the origin of the coordinate system For this model Equation (1) becomes

$$V_j(t) = \sum_{i=1}^{N} F_i(t) \cos\theta_{ij} \qquad (2)$$

where

$V_j(t)$ is the potential measured at point j at time t

$F_i(t)$ is the magnitude of the i-th dipole moment at time t

$\cos\theta_{ij}$ is the cosine of the angle that the i th dipole axis makes with the j ith axis, and

N is the number of dipoles.

Note that

$$\cos\theta_{ij} = \Psi_{ij}$$

where Ψ_{i1}, Ψ_{i2}, Ψ_{i3} are the direction cosines of the i-th dipole axis. The physical situation for the i-th dipole and the j-th observer at some time t is indicated in Fig 8

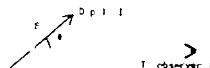


Fig 8 The physical situation of Model 1 The medium is infinite relative homogeneous. This model considers the heart as an equivalent dipole I neither distance nor ... effect ... sidered

In Model 2 the medium was again considered to be homogeneous and of infinite extent However the observers were placed at finite distances from the heart and hence the heart could no longer be thought of as a point. Let the coordinates of the j-th observer be (y_1 y_2 y) and the coordinates of the i-th chamber be (x x_{2i} x i) Then the dipole formula for N time varying dipoles

$$V_j(t) = \sum F(t) \frac{\cos \theta_{ij}}{r^2} \quad (3)$$

becomes

$$V(t) = \sum^{N} F(t) \frac{\sum \Psi (y - x_m)}{\left[\sum (y - x_m)^2\right]^{\frac{3}{2}}} \quad (4)$$

where Ψ_1 Ψ_2 Ψ_3 are the three direction cosines of the i th moment vector The physical situation is shown in Fig 9

For Model 3 we refer to the paper by Wilson and Bayley In order to study the effects of eccentric dipoles in a bounded medium it was decided to use the mathematically simple expressions derived in that paper for a spherical volume conductor of constant resistivity The potential at a point P on the surface of the conducting sphere of radius R due to an eccentric dipole is

$$V_P = \frac{F}{R^2} \sum \Psi \left(\frac{2(\lambda_m - f l_m)}{(1 + f^2 - 2f\gamma)} + \frac{(f - \gamma)\lambda_m - (f\gamma - 1) l_m}{f(1 - \gamma)(1 + f^2 - 2f\gamma)^{\frac{1}{2}}} + \frac{\gamma \lambda_m - l_m}{f(1 - \gamma)} \right) \quad (5)$$

The position of the dipole is given by a radius vector of length fR and direction cosines l_1 l_2 l_3. The dipole moment is of magnitude F and has direction cosines Ψ_1 Ψ_2 Ψ_3. The radius vector to the observer is, of course of length R and the direction cosines are λ_1 λ_2 λ_3. The angle between the radius vectors to the dipole and to the point P has cosine

$$\gamma = \sum \lambda_m l_m \quad (6)$$

The potential is taken relative to some fixed reference point For N dipoles with time varying moments, this equation becomes for some observer j

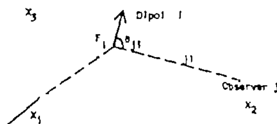


Fig 9 The physical situation of Model 2. Observers are stationed in an infinite homogeneous, resistive medium. Each of the 20 dipoles is stationed at the centroid of the myocardial segment that it represents. Distance effects from the 20 dipole heart to Cube system of electrode placement are then computed.

$$V(t) = \sum_{i=1}^{N} \frac{F_i(t)}{R^2} \sum \Psi \left(\frac{2(\lambda_{mj} - f_i l_{mi})}{(1 + f^2 - 2f_i\gamma)} + \frac{(f_i - \gamma_{ij})\lambda_{mj} - (f_i\gamma_{ij} - 1) l_{mi}}{f(1 - \gamma)(1 + f^2 - 2f_i\gamma)^{\frac{1}{2}}} + \frac{\gamma \lambda_{mj} - l_m}{f(1 - \gamma_{ij})} \right) \quad (7)$$

The situation is indicated in Fig 10 In the figure S is the center of the sphere The x y and z axes, and the X Y and Z electrode positions are also indicated

Equations (2) (4) and (7) may be written in the form

$$V(t) = \frac{1}{R^2} \sum_{i=1}^{N} F_i(t) C_{ji} \quad (8)$$

where

$V_j(t)$ is the potential observed by the j th observer at time t

$F_i(t)$ is the magnitude of the dipole moment of the i th chamber of the heart at time t

C_{ji} is a constant associated with the i th dipole and the j th observer

R is the radius of the sphere for a spherical volume conductor otherwise R may be set equal to one

By comparing Equation (8) with Equation

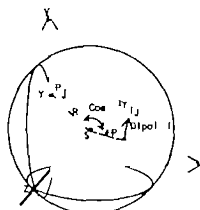


Fig 10 The physical situation of Model 3 Observers are stationed on the surface of sphere at 4 corners of cube. The 20-distributed-dipole heart is eccentrically placed in homogeneous sphere I this simulation both distance and boundary effects are computed, simulating a Cube ectorcardiogram.

(2) (4) and (7) we see that the constants C are for Model 1

$$C = \Psi \quad (9)$$

for Model 2

$$C_i = \frac{\Sigma \ \Psi \ (y \ - x_n)}{\left[\Sigma \ (y \ - x_n) \right]^{i}} \quad (10)$$

and for Model 3

$$C = \Sigma \ \Psi \ \frac{2(\lambda_n - f_i l_n)}{(1 + f - 2f \ \gamma_i)^{3/}} \quad (11)$$

$$+ \frac{(f - \gamma) \lambda_n - (f \gamma - 1) L_n}{f (1 - \gamma)(1 + f^2 - 2f_i \gamma)^{1}}$$

$$+ \frac{\gamma_i \lambda_n - L_n}{f_i (1 - \gamma_{ij})}$$

In these equations,

Ψ_1 Ψ_i, Ψ_i are the direction cosines of the i th moment vector

x_{1i}, x_i x are the coordinates of the i-th dipole

y_{1j} y_j y_{3j} are the coordinates of the j-th observing electrode and in Equation (11)

$$f_i = \frac{\left[\Sigma \ (x_n - S_n) \right]^{1}}{R} \quad (12)$$

$$l_{ki} = \frac{x_k - S_k}{\left[\Sigma \ (x_n - S_n)^2 \right]^{1}}$$

$$\lambda_j = \frac{y_{kj} - S}{R}$$

$$\gamma = \Sigma \ L_n \lambda_n$$

where S S_2 S_3 are the coordinates of the center of the sphere. The potentials relative to the fourth observer are

$$[V(t)]_{rel} = V(t) - V(t)$$

for the three observers j = 1 2 3

These are the x, y and z components which when appropriately plotted produce the simulated vectorcardiograms.

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Case reports

Bilateral pheochromocytoma The application of a plasma catecholamine bioassay for tumor localization

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J F Glenn M.D
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Du ham N C

Preoperative localization of pheochromocytoma has been accomplished by intravenous or retrograde pyelography aortography and retroperitoneal gas insufflation contrast studies. Localization of these tumors by assaying venous blood for catecholamines obtained by vena caval catheterization was first described by von Euler and associates in 1955 Since that time, 19 other cases ha e been described in which chemical assay of plasma catecholamines obtained by venous catheterization has aided in the preoperat e localization of these tumors (Table I) This report describes the first use of the spirally cut rabbit aortic strip in the bioassay of plasma catecholamines for the purpose of localizing a pheochromocytoma in a young patient who presented a number of atypical and unusual clinical features

Case report

S. D 12-year-old h male was fir admit ed t the Duke University Medical Center on Dec 29 1963 for the evaluation of levated urinary catecholamines One ear prior t admission the patient no l intermittent, bitemporal, throbbing head aches relieved by rest or salicylates T months prior to this first Duke Hospital admission, an ppendectomy as performed the local hospital for cute ppendicitis and routine bdominal ex plora ion tha time as said be normal N ide fluctuations in blood pressure ere oted However postopera ely the patient xperienced ather prof se sw ting and sensation of generally "feeling bad the absence of ber systemic or local symptoms On Nov 12 1963 h was read mitted to his local hosp al for the evaluation of ague joint pai 15 pound eight loss and episodic eating *Past medical history family* history and systems review were negativ for hypertension nd endocrinopa h Physical examination (Nov 12 1963) revealed supine blood pressure f 119 84 mm Hg both arms and 170 130 mm Hg in the right leg The right optic disc as blurred medially but f ndoscopic examination was otherwise negativ The heart was not enlarged nd no murm rs ere dible Abdominal examination w normal and no objectiv joint abnormalities ere observed C fé la spot ere no present.

Laboratory studies including complete blood ount fasting blood sugar blood urea nitrogen, and serum electrolytes ere normal T tal phenol sulfonphthalein excretion as 91 per ent in 2 hours The rine ontained 1+ protein bu as otherw se normal The ra enous pyelogram electror rdio

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Table I

Author	*No. of patients*	*Localized by other diagnostic procedures*		*Localized by venous sampling*
		Yes	*No*	
von Euler and associates	1	0	1	1/1
von Euler and Ström[3]	2	2	0	2/2
Crout and Sjoerdsma[3]	5	0	5	4/5
Vendsalu[4]	4	1	3	4/4
Mahoney and associates[5]	5	0	5	4/5†
McGuire and Fox	1	0	1	1/1
Flesher and associates	1	0	1	1/1
Duke and associates	1	0	1	1/1
Present case	1	0	1	1/1
Total	21	3	18	19/21
Per cent	100	14	86	90

*One patient had no sharp increase in catecholamine levels and was assumed to have constant, but minimal secretion.
†One patient had diffuse metastases and elevated values all along the inferior vena cava.

Table II

Date	*Urinary epinephrine (µg/24 hr.)*	*Urinary norepinephrine** (µg/24 hr.)*	*Urinary VMA†*
1963			
November		850‡	
		415	
		2000	
December 30	29	2285	
December 31	0	1876	
1964			
January 6	5	646	
January 11	Left pheochromocytoma removed		
February 6	0	547	
July 9	5	339	
December 28	0	553	13 5
1965			
January 15	Exploration negatn		
April 10	23		7
December 28	—		
1966			
April 17	10		
April 18	0		
May 16	0		
May 18	Right pheoc.		
May 22	8		
October 31	25		
November 1	14		

*Determined by the method of von Euler and Lishajko. ... hours.
†Determined by the method of Pisano, Crout, and Abraham.[8]
‡Determined by Biochemical Procedures, N. Hollywood, Calif.

gram, chest x-ray and electroencephalogram were normal. Three 24 hour urine collections disclosed markedly elevated catecholamine values (Table II). The demonstration of elevated urinary catecholamine excretion prompted referral to Duke Hospital for further evaluation and treatment.

One week prior to this scheduled admission after a period of strenuous exercise, the patient experienced a brief episode of diaphoresis, weakness, and pallor.

Physical examination (Dec. 29, 1963) at the time of his first Duke Hospital admission revealed a blood pressure of 126-142/84-90 mm. Hg in both arms supine, 126/80 mm. Hg standing, and 146 mm. Hg by palpation in the right leg. The remainder of the physical examination was within normal limits except for slight blurring of the medial portion of the right optic disc.

Routine urinalysis, complete blood count, fasting blood sugar, blood urea nitrogen, serum electrolytes, total serum protein, and albumin were all within normal limits. An intravenous pyelogram was normal, but a perirenal carbon dioxide (93 per cent) insufflation study suggested a left suprarenal mass. Urinary catecholamine determination (Table II) documented elevated norepinephrine and normal epinephrine excretion. Abdominal exploration on Jan. 6, 1964, revealed a 3 × 3 × 3 cm. pheochromocytoma in the left adrenal gland. The tumor and left adrenal gland were removed en bloc. The abdominal sympathetic nerve chains as well as the right adrenal area were explored and no additional tumors were found. No wide fluctuations in blood pressure were noted during operation; blood pressure ranged from 150/110 mm. Hg to 120/90 mm. Hg throughout the remaining 9 days of this hospitalization. Five days postoperatively the urinary norepinephrine level was 646 μg per 24 hours. He was discharged on no medications to be followed in the outpatient clinic.

One month later at the time of his first postoperative outpatient visit, the blood pressure was 120/76 mm. Hg. Occasional headaches persisted, but were decreased in frequency and intensity. Urinary norepinephrine excretion was 547 μg per 24 hours. Approximately 2 months postoperatively the patient complained of insomnia and nightmares which responded to mild sedation. A weight gain of over 30 pounds had occurred and blood pressure of 124/82 mm. Hg was observed.

Six months following his adrenal operation the patient again noted several transient episodes of flushing and palpitation after strenuous exercise. The blood pressure was 110/70 mm. Hg and urinary norepinephrine excretion was again above the limits of normal (339 μg per 24 hours).

On Dec. 28, 1964, 11 months after adrenal operation, the patient was readmitted because of increasing fatigue, episodic palpitations, and "leaden legs." During this hospitalization, multiple daily blood pressures ranged between 100-110/60-80 mm. Hg and the physical examination was within the limits of normal. The previously described blurring of the right optic disc had cleared. Routine laboratory studies including a repeat intravenous pyelogram were all normal. A histamine provocative test was within normal limits. On this admission, urinary norepinephrine was again elevated as was the vanillylmandelic acid (VMA) excretion. Cystoscopic examination revealed no evidence of vesical pheochromocytoma (paraganglioma). In an attempt to localize the source of increased urinary norepinephrine excretion, retrograde femoral vein catheterization was performed and multiple blood samples were obtained along the course of the femoral vein, iliac vein and vena cava. The samples were analyzed for catecholamines according to the method of von Euler. No definite elevation of plasma catecholamines could be demonstrated. These samples were obtained at a time when urinary norepinephrine levels were elevated.

On Jan. 15, 1965, approximately one year after the removal of the pheochromocytoma on the left, repeat abdominal exploration was accomplished with no demonstrable tumor. The right adrenal gland was normal to palpation and no wide fluctuations in the blood pressure were noted. At 3 and 11 months after the second abdominal exploration, urinary norepinephrine or VMA levels remained elevated. The patient was asymptomatic and normotensive on no medications.

On April 15, 1966, 14 months after the second exploration, the patient was readmitted with a 36 hour history of abdominal pain without other associated symptoms. The blood pressure was 118/84 mm. Hg supine and 120/86 mm. Hg upright. Physical examination and routine laboratory studies were normal. An electrocardiogram demonstrated left ventricular hypertrophy. Repeat intravenous pyelography was normal. Retrograde femoral aortography and selective renal angiography revealed questionable enlargement of the right adrenal gland. No definite tumor blush was visible. Urinary norepinephrine excretion remained elevated. The patient was discharged without further tests and on no specific therapy. During the 2 weeks following discharge, several episodes of postural syncope were observed and the patient was readmitted on May 16, 1966. The blood pressure was 125/90 mm. Hg with a pulse rate of 90 per minute in the supine position. In the sitting position, the blood pressure was 125/100 mm. Hg and the pulse rate increased to 140 per minute. In the upright posture the blood pressure was 125/100 mm. Hg with a pulse rate of 160 per minute and the patient complained of dizziness. The remainder of the physical examination was again normal as were the routine laboratory studies. Special procedures included the estimation of peripheral plasma catecholamines (rabbit aortic strip bioassay technique) in the supine posture and in response to progressive passive tilt to 70 degrees while also monitoring blood pressure, pulse rate, and the electrocardiogram. The results of this study are summarized in Fig. 1. In addition, 4 days later retrograde femoral venous catheterization was performed and venous samples obtained from multiple sites along the vena cava for plasma catecholamine bioassay. These samples demonstrated a marked increase in vasoconstrictor material immediately above the renal veins (Fig. 2). On the basis of these findings, together with the continued elevation of urinary norepinephrine levels, repeat abdominal and retroperitoneal exploration was performed on May 18, 1966, with

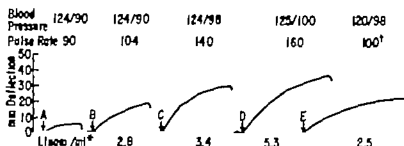


Fig. 1. Demonstration of increasing plasma concentration of peripheral vasoconstrictor material in response to passive tilt to 70 degrees. Points A through D represent points in progressive tilt from supine posture to 70 degrees. Point E is 3 minutes after return to the supine posture. The curves are tracings of the deflection (mm.) produced by the aortic strip preparation in response to individual aliquots (0.3 ml.) of peripheral plasma. *Estimated plasma catecholamine concentrations (see text). † followed by a short period of sinus arrest with nodal escape and subsequent return to normal sinus rhythm at 66 per minute.

particular interest being directed to the right side box the right renal vein. A tumor 2 cm. in diameter was located behind the inferior vena cava medial to the right adrenal gland and attached to the gland by a thin stalk of tissue. The tumor and the medial half of the right adrenal gland were removed. The postoperative course was benign. Since discharge the blood pressure was continued to be variably elevated and multiple urinary catecholamines have been normal. The symptoms of fatigue, sweating, and postural syncope have disappeared. Intermittent headaches and abdominal pain persist. The patient is currently doing well and following ACTH stimulation and withdrawal of steroids has normal adrenal function from the remaining right adrenal remnant.

Methods and results

The bioassay of plasma catecholamines was performed utilizing the spirally cut rabbit aortic strip prepared as described by Helmer. Heparinized venous blood was collected and placed immediately in an ice slush, centrifuged, and the removed plasma placed in ice and kept cold until the time of assay on the same day of this collection. Equal plasma volumes (0.25 to 0.3 ml.) were assayed in duplicate from each sampling site. The responses of the individual plasma samples were bracketed with an equiconstrictor amount of norepinephrine (levarterenol bitartrate) standard prepared in 0.001N HCl for estimation of the concentration of constrictor material contained in the plasma unknowns. A titration and dose response curve was utilized to demonstrate continued stability and responsiveness of the bioassay preparation. Equal volumes of all individual plasma samples were reassayed following adsorption with aluminum oxide (pH 3.4) to effect the removal of endogenous catecholamines. Further evidence that the constrictor material present was catecholamines was demonstrated by the blocking action of phentolamine during peak contraction of the test samples and the failure of the aortic strip to respond thereafter to added amounts of known norepinephrine standard and active plasma. The ability of the aortic strip to respond to other (non-alpha receptor-dependent) vasoactive materials was shown by a prompt constrictor response to synthetic angiotensin II.

Urinary catecholamines were measured by the method of von Euler and Lishajko.[9]

Fig. 1 illustrates the presence of increasing amounts of vasoconstrictor substance in peripheral plasma in response to a progressive passive tilt to 70 degrees. This finding occurred in conjunction with increasing pulse rate without a change in blood pressure followed by near syncope at the peak of the tilt which necessitated return to the supine posture and was then associated with a rapid decrease in the concentration of this vasoconstrictor material and subsidence of the previous symptoms. These data are felt to represent an exaggerated response of the previously reported normal increase in plasma levels of catecholamines in response to changes in body posture[11] in this patient with a norepinephrine secreting pheochromocytoma.

The anatomic site and bioassay results

Hypertensin—Ciba, Ciba Pharmaceuticals, Summit, N. J.

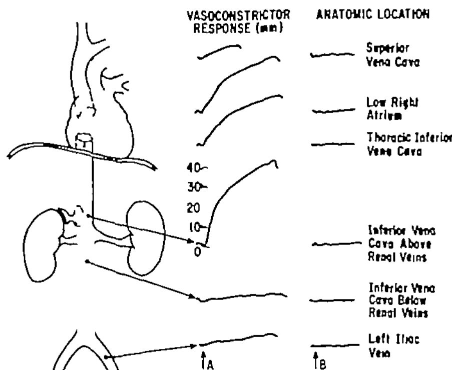


Fig 2 Demonstration of increased plasma concentration of vasoconstrictor material below the renal veins. At point A, the curves are tracings of the deflection (mm.) produced by the aortic strip preparation in response to the addition of 0.3 ml. of plasma collected from the specified sites along the vena cava. At point B equal volumes of plasma (0.3 ml.) were added following adsorption with aluminum oxide pH 3.4 (see text)

of plasma samples obtained at the time of the second retrograde femoral venous catheterization are shown in Fig 2. These data demonstrate a marked increase in vasoconstrictor material just above the entrance of the renal veins into the inferior vena cava. This finding in conjunction with the usual anatomic location of the right adrenal vein were considered to provide evidence for the presence of increased catecholamine release from the area of the right adrenal gland (particularly since the left adrenal had been previously removed) and this was confirmed at the time of operation with the demonstration of a small pheochromocytoma attached to this gland

Discussion

This patient presented a difficult and somewhat unusual problem in the diagnosis of pheochromocytoma. He was normotensive at a time when the urinary catecholamine excretion was at its highest level. Later in his course even though variably hypertensive his blood pressure was only minimally elevated. These findings have been observed by others,[n n] but this represents a relatively low incidence or rare finding in the reported cases of pheochromocytoma. His predominant symptom was headache a common and important symptom in pheochromocytoma. The infrequent but definite, episodes of flushing palpitation sweating and weakness are also suggestive of pheochromocytoma. The presence of postural syncope has been only occasionally reported by most investigators,[n] although Kirkendall Liechty and Culp[1] noted syncope in 39 per cent of 18 patients with pheochromocytoma. However in contrast to the present patient other reported cases have exhibited postural hypotension in association with syncopal attacks.

The presence of bilateral pheochromocytomas in this patient is of special importance and points out the need for precise localizing preoperative d tic in these patients. It m in

of preoperative vena caval catheterization with the measurement of plasma catecholamines may offer the necessary accuracy as a diagnostic tool in these patients. Table I summarizes the present report and all previous reported cases of attempts at tumor localization by venous sampling for sites of increased plasma catecholamine levels. Importantly, of the 18 cases that were not localized by the usual diagnostic procedures, 16 or 89 per cent were localized by vena caval sampling. The remaining 2 cases were of such an unusual nature that all localizing diagnostic studies failed.

It is the purpose of this report to describe the use of the spirally cut rabbit aortic strip in the estimation (bioassay) of plasma catecholamines and its application in the localization of a second elusive pheochromocytoma in this patient. Helmer[19] has previously described the use of this technique for urinary catecholamine determinations and his observations have been extended and confirmed by Heineman and Danowski.[8] To our knowledge no one has reported the use of this technique for the estimation of plasma catecholamine levels in man. Except for the first report by von Euler and associates,[1] in which a bioassay technique was used, all previous plasma catecholamine measurements for similar studies[2-8] have used one or more of the well-known fluorometric or chemical techniques which are quite tedious and not widely available. In contrast, the aortic strip technique is not technically difficult and requires only minimal inexpensive equipment available in most laboratories. The assays can be performed quickly and reproducibly with semiquantitative results. The definition of the material assayed may be substantiated by biologic, physical, and pharmacologic means as previously outlined. These features also suggest the possible use of this bioassay technique at the time of operation for more precise tumor localization.

This patient demonstrated an increasing peripheral venous plasma concentration of vasoconstrictor material in response to a progressive passive tilt to 70 degrees; this was associated with near syncope and tachycardia. On return to the supine position all symptoms disappeared along with a decreased concentration of this circulating vasoconstrictor material which on bioassay was compatible with a catecholamine. More importantly, at the time of venous catheterization a sharp increase in plasma vasoconstrictor material appeared at the anatomic localization of the right adrenal gland. It is important to note that an earlier study utilizing chemical catecholamine determinations, performed in another laboratory, failed to demonstrate an increased concentration of pressor amines at this point; this former study was also performed at a time when urinary catecholamines were increased.

In view of the potential multiple anatomic sites in patients with pheochromocytoma, particularly in children,[9,13,21-24] the reported morbidity and mortality of other studies (arteriography and CO_2 insufflation)[27,28,29] used to localize pheochromocytomas and the relatively benign nature of venous catheterization together with the accuracy in this and other reported cases, it would appear that venous catheterization with the measurements of plasma catecholamine levels seems indicated and a procedure of choice in the preoperative evaluation of most patients with pheochromocytoma. As suggested by Crout and Sjoerdsma, this is particularly important if previous operation has been negative and when an extra-abdominal tumor is present in a patient with the chemical diagnosis of pheochromocytoma.

Precise intra-abdominal localization using this technique should minimize the amount of tedious dissection through scar tissue and adhesions in patients that have been previously explored. However, abnormal venous drainage of the tumor can be misleading, as in the case of von Euler and associates.[1] Preoperative localization should also minimize the amount of palpation of the tumor and the consequent dangerous fluctuations in blood pressure that may occur.[30]

Summary

Report is made of a patient with bilateral pheochromocytoma in whom a bioassay of plasma catecholamines was useful in the localization of the tumor near and attached to the right adrenal gland.

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Paradoxic splitting of the second sound with transposition of the great vessels

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Paradoxic splitting of the second heart sound is almost always associated with significant heart disease. The usual mechanism is delay of the end of left ventricular ejection and can be seen with left bundle branch block, aortic stenosis, arterial hypertension, acute myocardial infection, and a patent ductus arteriosus.[1] Early activation of the right ventricle can also be responsible and is seen not uncommonly with Type B Wolff-Parkinson-White (WPW) syndrome.[2,3] Paradoxic splitting might also be expected if there were delay in mechanical events in a right ventricle which supplied the systemic circuit. The present case report describes such a set of circumstances in which paradoxic splitting was demonstrated.

Case report

A diagnosis of complete transposition of the great vessels was made shortly after birth. Cyanosis was intense, growth and development were poor, and at 16 months of age an atrial septectomy was performed. Considerable improvement ensued but by 8 years of age cyanosis was again intense and physical capability severely impaired. A short Grade II systolic murmur was heard at the mid left sternal border, an early systolic click was present along the left sternal border, and the second sound was loud and single at the base. Hemoglobin was 22.4 Gm. per cent and hematocrit 65 per cent. An ECG showed severe right axis deviation, right ventricular hypertrophy, and right atrial enlargement (Fig. 1). Cardiac catheterization was carried out and complete transposition of the great vessels was confirmed. Bidirectional shunting was demonstrated at atrial level. A small ventricular septal defect was found and a small right-to-left shunt was seen at ventricular level. Mean pressure in the main pulmonary artery was roughly two thirds of the mean pressure in the aortic root. Hemodynamic correction was carried out on the pump oxygenator by the technique described by Mustard[4] and the small ventricular septal defect was closed. Right bundle branch block appeared during the procedure (Fig. 2). Postoperatively splitting of the second heart sound was evident for the first time and the split narrowed during inspiration. External phonocardiography with simultaneous carotid arterial pressure tracing showed aortic closure following pulmonic and confirmed narrowing of the splitting with inspiration (Fig. 3). Six months after surgery the boy had gained 7 pounds, was acyanotic and asymptomatic, and was permitted full activity short of competitive sports.

Discussion

Splitting of the second heart sound has been known for at least 100 years. Normally aortic closure precedes pulmonic

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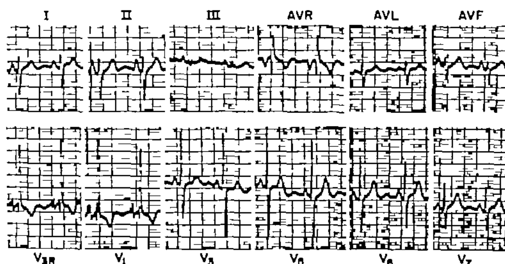


Fig. 1 Preoperatn electrocardiogram showing severe right xis deviation right entricular hypertrophy and right trial enlargement.

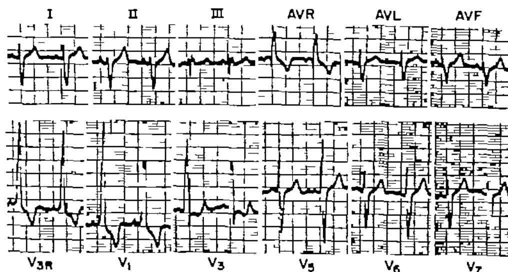


Fig 2 Postoperatl electrocardiogram There continues to be severe right xis deviation and right entricula hypertrophy QRS duration has increased and evidence of right bundle branch block is present.

and since pul nonic closure is delayed by the increase in right ventricular stroke volume which occurs during nspiration the split should alwa s widen w th inspira tion Paradoxic splitting implies that pul monic closure precedes aortic and there fore that the split narrows w th inspiration The majority of reported instances of pa adoxic pl tting i volve a d lay in left ventricula mecl n l events I robably the commonest cause is left bundle branch block but paradoxic splitt ng is not rare in severe aortic stenosis and is well recog nized w th occasional cases of patent ductu arteriosus with arterial hyperten sion and with acute myocardial infarction

March and co-workers documented par adoxic spl tting n a single case of WPW syndrome and Zuberbuhler and Bauersfeld added three more case reports. Early

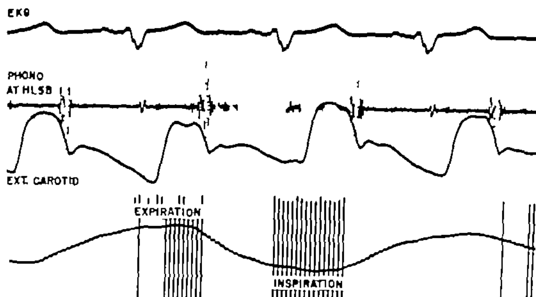


Fig. 3. Postoperative phonocardiogram with simultaneous carotid pulse tracing and pneumograph. Splitting of the second heart sound is evident with expiration and aortic closure follows pulmonic.

electrical and mechanical events in the right ventricle resulted in early pulmonic closure in Type B WPW syndrome. Paradoxic splitting has not been seen with Type A WPW syndrome which is thought to involve early activation of the left ventricle.

Right bundle branch block usually results in late closure of the pulmonic valve and therefore in a widely split second sound. In the case presented above complete transposition was present and therefore the aorta arose from the right ventricle. Preoperatively the second sound was single and presumably aortic and pulmonic closure were nearly simultaneous. Hemodynamic correction was obtained by the Mustard technique in which an atrial baffle is constructed of pericardium. Systemic venous return is routed to the left atrium, left ventricle and pulmonary artery. Pulmonic venous return is directed to the right atrium, right ventricle and aorta. Thus unoxygenated blood perfuses the lungs and oxygenated blood is distributed to the systemic circuit. Postoperatively a right bundle branch block was present and splitting of the second sound was first appreciated. The split clearly narrowed in inspiration and a simultaneous carotid pulse tracing showed that aortic closure followed pulmonic. Since right ventricular events were delayed by the bundle branch block and since the right ventricle communicated with the aorta such delay caused aortic closure to follow pulmonic and resulted in narrowing of the split with inspiration.

Summary

Previously described causes of paradoxic splitting of the second heart sound have included late activation of the left ventricle and early activation of the right ventricle. Paradoxic splitting may also result from late activation of the right ventricle if complete transposition of the great vessels is present. Such a case with complete transposition, right bundle branch block, and paradoxic splitting of the second heart sound is presented.

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Clinical pathologic conference

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Clinical abstract

DR THOMAS COOGAN SR This patient 28-year old Caucasian male executive was admitted to the hospital because of decreasing exercise tolerance. He complained of a chronic cough made worse by lying flat. He had had an essentially healthy childhood until 1948 when his physician detected a heart murmur. Electrocardiograms, cardiac fluoroscopy and the like were negative. In 1957 he sustained injury to his thorax in an automobile collision in which the steering wheel was broken by impact with his chest. X-rays of the chest were negative. In 1962 x-rays showed slight enlargement of the left side of the heart. In 1964 approximately 18 months prior to this admission he developed a nonproductive cough and general malaise. His weight, which had increased to 197 pounds from a normal of 175 was reduced by diet to 176 pounds. In November 1964 he noted diminished exercise tolerance with cough and expiratory rattle. X-rays disclosed cardiomegaly. Electrocardiograms revealed left ventricular and left atrial enlargement and tachycardia. Hospital admission was recommended but was refused by the patient. On the day before hospital admission in January 1965 tachycardia, cardiomegaly and small lateral pulsations of the heart on fluoroscopy were noted. Electrocardiographic studies revealed left axis deviation with partial left bundle branch block.

His past history involved extensive traveling. In 1948 he was in Cuba and Guatemala traveling in the interior for t days. In 1950 he was in Jamaica, the Dominican Republic, Venezuela, and Trinidad. In 1952 he was in Panama and Colombia. In 1954 he visited the Virgin Islands and traveled through South America. In 1956 he toured Europe. Between 1959 and 1962 he visited the Mediterranean, the Eastern African Coast and the Persian Gulf while in Naval Service. He denied any illness during these excursions. He admitted moderate alcoholic intake while in the Navy. After discharge from the Navy in 1962 he drank 2 to 3 cocktails a day. He smoked 3 packs of cigarettes each day until July 1963. During his military life he drank as many as 20 cups of coffee per day. Chest x-rays yielded no significant findings.

Electrocardiograms taken during his first hospital stay in January 1965 indicated left atrial enlargement. Partial left bundle branch block was recurrent and delayed A V conduction was present at times. Admission electrolytes were serum sodium 146 mEq per liter potassium 4.6 mEq per liter chlorides, 107 mEq per liter and CO 28 mEq per liter. Serum glutamic oxalacetic transaminase (SGOT) was 32 lactic dehydrogenase (LDH), 28. Creatinine was 1.2 blood urea nitrogen (BUN), 15; calcium, 9.2 phosphorus, 4.3 mg per 100 ml. Postprandial blood sugar was 123 mg per 100 ml. Hematocrit was 47 per cent. Hemoglobin was 15.8 Gm per cent white blood count (WBC) 8 600 per cubic millimeter total eosinophil count, 168 per cubic millimeter. Sedimentation rate was 1. C-reactive protein was negative. Serum iron was 67 µg. Total iron binding capacity was 378 µg. Urine (24 hour specimen) contained 50 mg of protein. Serum Kahn and Wassermann tests were negative. Alkaline phosphatase was 1.5. Thymol turbidity was 1.5. Serum protein electrophoresis was normal. Serum cholesterol was 224 mg per cent. A glucose-tolerance test revealed fasting blood sugar of 87 mg per cent; ½ hour 137; 1 hour 147; 2 hours, 134; 3 hours 138 mg per cent. All urine tests were negative. LE-cell preparations and Weil-Felix agglutinations were negative. ASO titer was 12 Todd units. Throat cultures revealed many α-Streptococci and Neisseria with few γ-Streptococci and Diplococcus pneumoniae. Heterophil agglutination test revealed titer of 1 14. Erythrocyte mass, plasma volume and blood volume were normal. T 3 uptake was 43.6. Sheep-cell agglutination test was normal. Acute and convalescent viral antibody titer studies revealed ECHO virus 9, Coxsackie A, Coxsackie B and adenovirus antibod

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t era of 1.8. Complement fixation test for Chagas disease was negative. Repeated blood cultures were negative. Skin tests for mycoses, trichinosis, and mumps were negative. Chest x-ray showed four chamber cardiac enlargement.

Several consultants found the same physical signs. There were diffuse right and left ventricle impulses. Blood pressure was 98/60, pulse rate, 112. P 2 was increased and there was gallop rhythm at the apex. There was a Grade III apical pansystolic murmur transmitted to the axilla. There was hepatomegaly of 4 cm. and questionable splenomegaly. There was question as to whether there might have been traumatic rupture of chordae tendineae of the mitral valve. The patient was digitalized and given mercurial diuretics. At the end of 6 days he had lost 13 pounds.

Cardiac catheterization on February 2, 1965 revealed marked mitral regurgitation with left ventricular dilatation and systemic hypotension secondary to low cardiac output. Left ventricular end diastolic pressure was elevated and there was early diastolic dip and plateau. Cineangiography revealed mitral regurgitation. Following diuresis he was recatheterized on February 25, 1965. Right heart pressures were normal at rest. Moderate pulmonary hypertension appeared with moderate exercise. Left ventricular end-diastolic pressures were high at rest and rose conspicuously with exercise. The low cardiac output at rest rose to normal resting value with exercise. Less evidence of mitral regurgitation was detected by cineangiography. Cardiac biopsy was considered but was rejected because of the risk.

When the patient left the hospital on March 20, 1965 he had lost 23 pounds. His heart rate was 100, blood pressure, 100/60. He was able to be flat without much discomfort. His heart size had diminished appreciably. Ultrasonic tests had revealed no sign of pericardial effusion. On cardiac fluoroscopy shortly before discharge the left ventricular pulsations were much better than on admission. He had developed left bundle branch block following catheterization and this was assumed to be due to the trauma of catheterization.

He was at home during the spring and summer of 1965. He was given Digoxin, 0.25 twice a day and 50 mg. of Hydrodiuril each morning. In May, 1965 because of the possibility of myocarditis, he was placed on Prednisone, 10 mg. 3 times a day with reduction to a maintenance dose of 5 mg. as needed. This was discontinued after 1 month because no improvement had occurred. On the first of August, 1965 he returned to work and soon was working full time. He felt quite well but his pulse rate was rapid. On August 12 his lungs were normal to auscultation. The heart was unchanged. Pulse rate was 108, blood pressure, 105/80. He was continued on Hydrodiuril and digoxin. His weight was 163 pounds. Prednisone was again given 10 mg. twice a day for the remainder of 1965.

In October, 1965 he attended a football game on a cold day. After that his cardiac reserve suddenly declined. He was given mercurial diuretics frequently and each time he would lose at least 6 or 7 pounds. After Christmas, 1965 he became increasingly short of breath and fatigued. He was hospitalized at complete bedrest for ten days. His pulse remained about 100. His lungs cleared and he felt somewhat better. He left the hospital on January 8, 1966. During this second hospital stay his heart was somewhat larger than on discharge in February, 1965. Medications were the same but steroid therapy was discontinued. It was suggested that he stop all intake of alcohol, as ingestion of small amounts seemed to worsen his condition. Electrocardiograms showed an increase in rate with no other change. Complete bundle branch block as well as evidence of digitalis effect persisted. Because of epigastric distress an upper gastrointestinal series was done and was negative. Postprandial blood-glucose levels were normal.

Two weeks later on January 16, 1966 he was readmitted to the hospital. According to his wife he had had a fever and Cheyne-Stokes breathing. Liver function tests were very abnormal: SGOT was 305, LDH 950, total bilirubin, 1.8. A diagnosis of hepatitis was made. A Bromsulphalein (BSP) test showed 77.9 per cent retention. The BUN was 46 mg. per cent. He had excreted little urine. On January 21 he had signs of hepatic coma. The SGOT was 2,820, total bilirubin 4, direct bilirubin, 2.2. Because of the coma, a spinal-fluid examination was done. This showed a slightly elevated ammonia content. The serum enzyme levels continued to increase: this indicated progressive acute liver necrosis. Reovirus, type 2, was assumed to be present, because an antibody titer of 1:256 was discovered on this admission. (Hepatitis virus was not isolated). On January 26 the BUN was 58 mg. per cent. Diuresis began and the mental state began to improve. On the next day the serum SGOT level declined to 1,100. Electrolytes were essentially unchanged, with a serum potassium of 6 mg. per cent. Prothrombin time was 30 per cent of normal. Total serum bilirubin was 5 mg. per cent on this day. On January 29 he had pain in the right midcalf. Heparin was started despite the low prothrombin time. On February 7 his total serum bilirubin was 1.8 mg. per cent, direct, 0.6 mg. per cent. BUN was 24 mg. per cent.

On February 14 after a restless night, he had a large bowel movement containing a large amount of barium. Subsequently he became increasingly short of breath. His blood pressure was 100/50. Soon he began to sweat profusely and blood pressure and pulse became unobtainable. He was unresponsive. The lungs were clear with no râles. The abdomen was soft without rigidity or tenderness. There was no calf or thigh tenderness. The skin was cool but moist. His color was ashen blue. An ECG showed sinus tachycardia with no axis shift. After blood had been drawn for glucose determination, 50 per cent dextrose in water was given intravenously. Within 25 minutes the patient began to improve and within 2 hours he had returned to his usual state. Blood glucose was 50 mg. per cent, sodium 131, potassium, 6, chloride 98 and CO_2, 11.2 mEq. per liter. Serum acetone was negative. Thus it appeared that the episode was due to hypoglycemia. On February 16 he had upper abdominal cramps, but there were no relevant findings. On February 18 he had abdominal pain in the left upper quadrant. On February 20 the BUN was 13, total serum bilirubin, 3.8; direct, 1.8 mg. per cent, and SGOT 86. On February 28, he again had a temperature rising to 100.6. Breath

sounds were diminished over the right lung base and there were moist râles at the left lung base. WBC was 11,950 per cubic millimeter. X-ray revealed an infiltrate in the right lower lobe posteriorly. Later that day his temperature rose to 100.6. He had a severe hacking dry cough with pleuritic right shoulder pain and blood-tinged sputum. The pulse rate was 120 and regular. Blood pressure was 95/85. Neck veins were distended. At this time it was agreed that he had a pulmonary infarct and heparin was again given.

On March 4 ligation of the inferior vena cava was recommended but permission was denied. On this day serum sodium was 115, potassium 4.9, chloride 81, CO_2 26.6 mEq. per liter and BUN 34 mg. per cent. On March 7 he coughed frequently and had difficulty in sleeping. X-rays revealed suprahilar infiltrates in both lungs, greater on the left side, and interpreted as due to recurrent emboli. On the next day severe epigastric pain occurred. Initially the bowel sounds were active, but soon they were absent. The pain was unrelieved by Maalox or atropine. Rebound was present. X-ray revealed air beneath the right diaphragm. At laparotomy a small perforation of the anterior wall of the duodenum was found. Approximately one quart of bile-stained, watery fluid was aspirated from the abdominal cavity. Gram stains showed only a few leukocytes and gram-negative bacilli. The ulcer was over-sewn and the abdomen closed with drains. Ventricular tachycardia along with multifocal premature ventricular contractions were noted during surgery. Blood pressure initially dropped to 70/40 but this rose and was maintained without vasopressor drugs at about 100/80. Shortly after midnight he was given I.V. mannitol in 50 per cent dextrose. He became anuric and his sensorium clouded. X-ray revealed new infiltrates in both lungs, presumably due to pulmonary emboli. Heparin was restarted. Arterial blood studies at 9:00 P.M. revealed a pH of 7.22 with a pCO_2 of 17.8. Because of progressive deterioration and severe acidosis, the decision was made to do peritoneal dialysis. This was begun at midnight. Despite temporary improvement, he died three days later.

Discussion

DR. THOMAS COOGAN, JR. We are presented with a well-traveled 28-year-old man who following 15 months of congestive failure developed hepatorenal failure, perforated duodenal ulcer, hypoglycemic episodes, and pulmonary emboli before he finally died. Our initial problem is the etiology of his heart disease. In childhood he had a murmur which after radiologic and electrocardiographic study was regarded as functional. Then there was a severe chest injury in an automobile accident eight years prior to his initial admission. Following this there seemed to be no heart murmur or cardiac enlargement. During the next few years he was in the armed services and passed the usual physical examinations. The first clue that anything was wrong with the heart was slight cardiomegaly detected by x-ray films 3 years prior to admission and 5 years after the automobile accident.

About 15 months before death there was generalized cardiomegaly, tachycardia with hypotension, a narrow pulse pressure, a loud third heart sound, and a murmur of mitral insufficiency. No paradoxical pulse or inspiratory swelling of neck veins was described. However, cardiac catheterization disclosed an early diastolic dip and plateau with a low cardiac output. These were most characteristic of restrictive heart disease. The signs of mitral insufficiency could be of rheumatic or traumatic origin or due to a dilated mitral valve ring secondary to enlargement of the left ventricle. If this were due to rheumatic fever, one would have to postulate an active carditis in view of the rapidity of its course and the amount of myocardial insufficiency. The absence of evidence of acute rheumatic fever, such as the normal sedimentation rate and the negative history of streptococcal infection, does not favor a diagnosis of rheumatic carditis. Traumatic sources of mitral insufficiency can be due to valve laceration or rupture of chordae tendineae or papillary muscles. After the rupture of a papillary muscle congestive failure usually evolves rapidly. It may be more delayed in onset with rupture of valve cusps or chordae tendineae but 8 years is a little long and during this period he passed military physical examinations. The murmur is best explained by dilatation of the mitral valve ring due to the large left ventricle. The marked decrease in mitral insufficiency during the second angiocardiogram, when the heart was better compensated, was additional evidence that the murmur was relative.

The restrictive heart disease could be at the pericardial, myocardial, or endocardial level. Constrictive pericarditis was unlikely in view of the very large heart and lack of calcification of the pericardium. The angiocardiogram and the ultrasonograms rule out significant pericardial effusion. The restriction was obviously at the endocardial or myocardial level. Endocardial fibroelastosis could produce this

picture but the age of onset rules out the primary form. If this were the secondary form we would still have to postulate a primary type of heart disease. This brings us to the myocardial source of the cardiac insufficiency. There was no evidence of hypertension or coronary artery disease so we are left with a myocarditis or myocardiopathy. There is much evidence against a myocarditis, including the lack of a recognized infection and lack of fever. The negative viral antibody titer studies, heterophil agglutination, complement fixation for Chagas disease, skin tests for mumps and trichinosis were evidence against some causes of myocarditis. A myocardiopathy is also more likely because of evidence of an enlarged heart 3 years before admission and survival for 15 months after the onset of congestive heart failure. Again, because of the clinical findings and laboratory data, we can eliminate as likely possibilities secondary forms of myocardiopathy such as those occurring in association with amyloidosis, sarcoidosis, scleroderma, hemochromatosis, and neuromuscular diseases. There was no heart disease in the patient's relatives, so we are inclined to eliminate familial forms. The late rapid liver failure does raise the question of lupus erythematosus, polyarteritis, and toxoplasmosis. The absence of rash, arthritis, significant abnormal urinary sediment, hematologic problems, and the negative LE preparations help to exclude lupus, while the low blood pressure and the lack of neuromuscular problems tend to exclude polyarteritis. Toxoplasmosis is more difficult to exclude. Infections early in life may cause myocardiopathy that becomes apparent in adulthood.

We are told that he enjoyed alcoholic drinks in moderation. It has been known for 70 years that ingestion of alcohol may favor development of heart disease. It can do it indirectly by replacing meals and leading to thiamine deficiency and beriberi. The second form is alcoholic cardiomyopathy. The pathogenesis of this disorder is not understood but it is assumed that alcohol interferes with membrane permeability and intracellular metabolism independent of effects due to thiamine deficiency. There can be mixed causes, and Alexander[4] has suggested that beriberi heart disease may be an early stage of alcoholic cardiomyopathy. The high cardiac output of beriberi due to peripheral shunts may be restored to normal output with thiamine. But as the disease progresses irreversible cardiomegaly, low output failure and increased peripheral vascular resistance dominate the picture. This is an intriguing idea but remains speculative.

The amount and duration of consumption of alcohol required for production of a cardiomyopathy are unknown. Evans[3] states that ingestion of a pint or more of spirits each day over a period of 10 years will injure the cardiac muscle. He also lists four types of T wave changes in the electrocardiogram and believes that they are characteristic but not necessarily diagnostic of alcoholic cardiomyopathy. They are the spinous or sharply pointed T wave, the dimple T wave, the cloven T wave and an inverted narrow T wave.

Now may I see the initial ECG tracing made before the patient developed the bundle branch block and before administration of digitalis? This tracing shows a sinus tachycardia. P waves are broad; this suggests left atrial enlargement. QRS complex is slightly widened; this suggests a parietal block. Voltage is high in precordial leads, probably indicative of left ventricular hypertrophy. However usual voltage criteria are not always meaningful with a parietal block. T voltage is decreased. QRS-T angle is abnormally wide possibly due to left ventricular hypertrophy. I cannot detect any of the T wave changes suggested by Evans as characteristic of alcoholic cardiomyopathy. Therefore in the absence of a history of excessive drinking, characteristic ECG changes, and evidence of decreased liver function at the time of his first admission, I cannot make a case for alcoholic cardiomyopathy.

One more cause that should be mentioned is cardiac contusion from the steering wheel accident with subsequent scarring and ultimate cardiac failure. Though I cannot exclude this, I would have expected greater cardiac functional impairment at the time of the injury.

I am afraid that I have been so diligent in ruling out known causes of cardiomyopathy that we are left with probable

the most common cause namely idiopathic myocardial hypertrophy and insufficiency.[14]

Now let us consider what happened to him after his initial admission. Despite digitalis, diuretics and prolonged bedrest during the next year he became more symptomatic and his heart size increased. He was given steroids without improvement. He then developed catastrophic acute hepatocellular disease and coma. At this time there was an elevated antibody titer for Reovirus No. 2 without isolation of the virus. The significance of this titer is questionable. This virus can cause encephalitis, hepatitis and rarely myocarditis in infant mice. Human infections are mainly in infants and I am not aware of the virus being defined as a cause of human myocarditis. There is no evidence of exposure to hepatic toxins or blood transfusions. Sudden portal hepatic vein thrombosis may begin this way but should also lead to rapidly developing enlargement of the spleen with ascites. The evidence points to an infectious hepatitis superimposed on a liver already injured by chronic passive congestion due to cardiac failure. Thrombophlebitis then developed, followed by hypoglycemic attacks. The latter were presumably due to severe liver disease with glycogen depletion. We are given no reason to suspect any other cause except possibly the hypoglycemia of early diabetes. The unusual glucose-tolerance curve a year earlier, with a low peak and continued elevations, suggests delayed or gradual gastric emptying.

He then proceeded to develop a series of pulmonary emboli which could have come from either heart or legs. Pulmonary emboli as well as systemic emboli coming from the heart are common in all forms of cardiomyopathy. He continued with a perforated ulcer, oliguria, uremia and finally death.

I conclude that he had (1) idiopathic myocardiopathy, (2) infectious hepatitis, (3) perforated duodenal ulcer and (4) terminal renal failure.

DR. HECTOR BATTIFORA: This 29-year-old man was well until 1957, at which time he had an automobile accident in which there was severe trauma to the anterior chest wall. A slight enlargement of the heart was noted at this time. In 1959 there seemed to be no further enlargement. In 1962, however, there was definite cardiac enlargement but there were no symptoms of cardiac insufficiency until the fall of 1964.

He was hospitalized in January 1965 to determine the cause of the myocardial insufficiency. He had a low cardiac output, a small pulse pressure and a large heart. Following catheterization he developed left bundle branch block. The reason for the cardiac enlargement remained obscure. In succeeding months he was given diuretics and digitalis. Cortisone was also used with the thought that he might have a myocarditis. He did not improve much.

In January 1966 he was readmitted to the hospital. At this time he was quite ill and febrile. It was concluded that he had hepatitis and he soon had signs of hepatic coma. There were several hypoglycemic episodes relieved by intravenous glucose. The explanation for these was obscure because previous blood-sugar levels had been normal. In the past he had complained of many episodes of sweating of unexplained origin and seemed to feel better after he had had a bottle or two of a cola drink.

In February 1966 he had pain in the muscles of the lower legs and it was determined that he had thrombophlebitis. Subsequently he had signs and symptoms of pulmonary embolism presumably secondary to venous thrombosis in the lower extremities. A few days later he had a perforated duodenal ulcer. After plication of the ulcer there was oliguria followed by anuria. He died on March 12, 1966.

The cause of the myocardial insufficiency was never apparent. A viral myocarditis seemed to be the most reasonable clinical explanation.

The autopsy showed enlargement (500 grams) of the heart with extreme dilatation of both ventricles and no valvular lesions. The coronary arteries had no stenosing atheromatous plaques or evidence of thrombotic closure. There was, however, at the apex of the left ventricle an aggregation of mural thrombi in various stages of organization. This type of intraventricular mural thrombosis is common

in patients with prolonged myocardial insufficiency especially when there is a great deal of associated dilatation of the ventricles. Ordinarily however mural thrombi at the apex of either ventricle under these conditions are not associated with extensive local myocardial disease In this case however there was extensive fibrosis of the myocardium at the apex of the left ventricle and adjacent septum over an area about 4 cm in diameter Also there were old and recent thrombi in the periprostatic veins, iliac venous tributaries, and distal pulmonary arteries. Infarcts were present in the periphery of the pulmonary parenchyma presumably due to embolization from peripheral venous thrombi secondary to the thrombophlebitis described clinically There were also several old and recent infarcts in the spleen adrenal and kidney These were undoubtedly secondary to embolism from mural thrombi at the apex of the left ventricle Another observation pertinent to the immediate cause of death was necrosis of the renal cortex with severe degeneration of the tubules due to prolonged hypotensive shock as well as mercurial medication The hepatocellular necrosis seemed best explained as viral in origin. There was some degeneration due to central passive congestion but anoxic congestion could not explain the necrosis in widespread areas other than those around central hepatic veins. Also, there was excessive stasis of bile in biliary canaliculi This is usually a

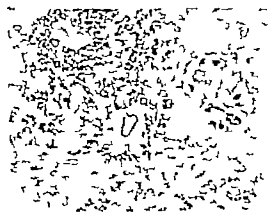


Fig 1 Photomicrograph of section of the pancreas showing hemangiectasis of the large islet of Langerhans. (Hematoxylin and eosin stain.)



Fig 2 Photomicrograph of an islet of Langerhans, showing the degree of hemangiectasis affecting all islets of the pancreas (Hematoxylin and eosin stain)

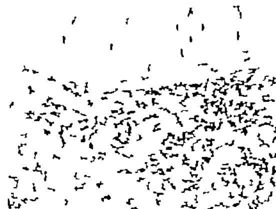


Fig 3 Photomicrograph showing granulation tissue arising from the endocardium and organizing mural thrombus at the apex of the cavity of the left ventricle of the heart. (Hematoxylin and eosin stain.)

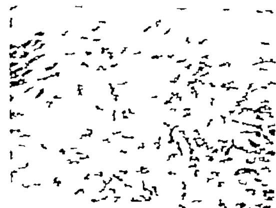


Fig 4 Photomicrograph of the myocardium at the apex of the left ventricle Note the extensive replacement of the cardiac muscle by dense scar tissue The myocardium at a distance from the apex normal. (Hematoxylin and eosin stain)

feature of viral hepatitis and is seldom associated with central necrosis due to shock or myocardial insufficiency. There was generalized peritonitis secondary to perforation of a duodenal ulcer and this contributed in a major way to the outcome.

One of the most interesting findings was the presence of miliary hemangiomas in lymph nodes, prostate and various fibrocellular tissues. There was also conspicuous hemangiomatosis or hemangiectasis of the islets of Langerhans (Figs. 1 and 2). The changes in the islets were of sufficient severity to lead us to the conclusion that this was a disorder which we have not seen before. I see no means of associating this with anything in the history except possibly the episodes of hypoglycemia, desire for cola drinks, or frequent sweats.

DR. GEORGE HASS. We have no adequate explanation for the entire clinical course. I believe that some findings bear upon the history and perhaps the myocardial insufficiency. These findings have to do with extensive apical scarring of the left ventricle with associated mural thrombosis and mesenchymal organization of thrombi (Figs. 3 and 4). The source of the myocardial damage is not clear. I suspect, however, that there was a traumatic source secondary to the myocardial contusion suffered years ago in an automobile accident. An alternate explanation is that with progressive myocardial insufficiency due to some other cause, mural thrombi might have formed spontaneously at the apex of the left ventricular chamber and that secondary myocardial damage occurred through coronary artery embolism from these mural thrombi. There is no proof of this, though there was substantial evidence of peripheral embolism into other arteries, especially those of the spleen, adrenal and kidney. The question arises as to whether this degree of scarring of the myocardium in an otherwise healthy man with an adequate coronary circulation could, together with the mural thrombi, produce the observed degree of myocardial insufficiency. I think that this is not likely unless there was some other factor. In seeking for this other factor, one would like to be certain that there had never been a bacterial infection of the mural thrombi which presumably formed at the apex following a traumatic hematoma and fibrosis of the left ventricular myocardium. In the event that there was bacterial localization in the thrombi, the possibility of myocardial insufficiency developing in the course of this type of sepsis might be regarded as analogous to toxic myocardial insufficiency of bacterial endocarditis or other chronic intermittent septicemias without significant structural valvular disease, myocarditis, or other apparent cause for myocardial failure.

Our best interpretation, therefore, is that apical myocardial scarring followed a severe anterior thoracic blow and myocardial contusion in 1957. Thereafter there was a local left ventricular apical aneurysmal dilatation and stasis which favored local formation of mural thrombi. These, in later years, became infected and toxic systemic effects secondary to mural bacterial ventricular thromboendocarditis led to myocardial insufficiency and peripheral embolism.

We are not familiar with the conspicuous hemangiectasis of the islets of Langerhans. All islets were involved. We assume that this was related to the miliary hemangiomata found in random microscopic sections of several organs. If so, the disorder is most likely of congenital origin. Whether excessive vascularity of islets induced a secretory abnormality which contributed to this bizarre syndrome is purely speculative but, in view of the rarity of this islet disease, we would be remiss in not drawing attention to its possible bearing upon the pathogenesis of the puzzling illness.

DR. REUBEN EISENSTEIN. I would like to ask Dr. Coogan, Sr., the attending physician in this case, if the patient had recurring fever and night sweats as a feature of his prolonged illness? If so, what attempts were made to determine the cause of these manifestations?

DR. THOMAS COOGAN, SR. The patient complained of some cold sweats both prior to his original hospital admission and during his hospital stay. I have carefully reviewed all of his records and there was no fever at any time except during the last admission when he had severe hepatitis.

Many blood cultures were done, all of

which were negative with one exception in which a staphylococcus was isolated but other blood cultures done on the same day were negative. The patient said he had no fever at home before entering the hospital

Many attempts were made to find petechiae or other evidence of subacute bacterial endocarditis, but all were unsuccessful

DR. ROBERT ALEXANDER Was there any evidence in the history that the patient was consuming anything other than the usual ingredients of cocktails which might have had a bearing on the production of a toxic myocardiopathy?

DR. THOMAS COOGAN SR There is absolutely no evidence in the history that the patient was consuming any unusual cocktails which might have had a bearing on the production of toxic myocardiopathy He drank a fair amount of whiskey and beer rather than mixed cocktails.

DR. RYOICHI OTASU Are you certain Dr Hass, that coronary thrombosis was not the primary cause of the extensive myocardial scarring restricted to the apex of the left ventricle and adjacent interventricular septum

DR GEORGE HASS I know of no case in which we have made a more thorough study of serial transverse blocks throughout the length of both coronary arteries and their branches. The coronary arteries were unusually free from disease for a man 29 years of age I suppose that embolic or thrombotic closure of the arterial supply to the apex of the left ventricle with complete repair and restoration of a normal arterial structure could have occurred. We have no proof of this, nor is it likely

DR. RAYMOND CLASEN Doctor Hass has emphasized the pathogenetic significance of myocardial contusion caused by sudden compression of the anterior thoracic wall by the steering wheel during the automobile accident several years before. Is injury to the myocardium a common result of such application of force and could it lead to the type of ventricular aneurysm with secondary mural thrombi found at autopsy? Why could not the destruction of muscle and fibrosis at the apex of the heart have been produced by bone-marrow or fat embolism to coronary arterial supply We frequently find bone-marrow embolism in the pulmonary arteries of patients whose chests have been struck forcibly in vigorous attempts to restart a heart which has ceased beating

DR. GEORGE HASS Impact of the type sustained in the automobile accident may cause myocardial contusion cardiac arrhythmia hemopericardium and even cardiac myocardial laceration There need be no fractures of the thoracic wall In accidents involving sudden deceleration of bony structure without equal deceleration of thoracic viscera, the forces productive of visceral injury are different from those due to a blow or compression. Once the force has produced the necessary degree of myocardial hemorrhage repair by fibrosis and secondary aneurysmal dilatation may be expected. As for myocardial infarction secondary to bone marrow or fat embolism due to the factors you mention, this is a possibility As a rule, however these embolic episodes seldom produce infarcts with the severe structural changes encountered in this case, unless there is an associated systemic circulatory insufficiency

DR. ROGER SMITH I am interested in the lantern slides which show the generalized enlargement of the islets of Langerhans and the capacious vascular channels between the cords of the islet cells. I have seen islets of this type occasionally in otherwise normal pancreatic tissue. Why do you Dr Hass, regard this as unusual or possibly significant in this case?

DR. GEORGE HASS All the pathologists who have studied the serial sections of this pancreas are unable to recall having seen a disease of this nature The plexiform angiomatous vascularity of all islets is exceptionally impressive. This leads to a consideration of the possibility of some abnormal secretions of glucagon insulin or other substance. Could the excess periodic flux of blood through these islets lead to hypoglycemic symptoms due to hyperinsulinemia or to hyperacidity and duodenal ulcer by mechanisms involved in the Zollinger Ellison syndrome Also I do not know if cardiac failure in this case might have been favored by multiple peripheral vascular shunts. Ordinarily these lead to high cardiac output but in late stages a low-output failure may develop

In recent months we have been seeking similar changes in routine autopsy material. Thus far we have found nothing other than occasional islets with dilated vascular channels, but these do not resemble the hemangiectasis of islets noted in the pancreas of this case.

DR. JOHN SYVER: Does the pathologist recognize alcoholic cardiomyopathy as an entity distinct from the cardiomyopathies of *nutritional deficiencies*. Certainly the great majority of people addicted to alcohol with or without cirrhosis of the liver do not suffer unduly from chronic myocardial insufficiency. Furthermore autopsies on the great majority of these cases do not disclose an impressive frequency of idiopathic cardiac hypertrophy and chronic myocardial failure. It seems to me that most of our patients at autopsy who have idiopathic cardiac hypertrophy with chronic myocardial failure were not alcoholic patients. Dr. Hass, is this correct and how do you distinguish the alcoholic from the nonalcoholic idiopathic cardiomyopathies?

DR. GEORGE HASS: You are correct and I don't.

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Fundamentals of clinical cardiology

Acute pulmonary embolism

II Clinical

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Part I of this paper covered the problem of acute pulmonary embolism from the standpoints of incidence predisposing factors, pathogenesis, normal pulmonary structural and functional relationship and pathophysiologic manifestations.

Clinical manifestations

Although thrombosis in the deep veins of the lower extremities is the commonest source of pulmonary emboli t is worth re-emphasizing that clinical vidence of pulmonary embolism commonl occurs without clinical evidence of thrombophlebitis before or after the embolic episode. Thus, Barker and co-workers[34] found no clinical evidence of th ombophleb tis in 45 per cent of cases of post operative fatal pulmonary embolism and no clinical or postmorten e idence n 40 per cent. In only 15 per cent did linical evidence of thrombophleb tis preced death from pulmonary embolism and in only 5 2 per cent was iliofemoral phlebitis diagnosed before symptoms of embolism occurred

These findings are readily understood. A small nonlethal embolus may arise from a thrombus too deep and too small to detect A large lethal embolus may arise from a thrombus above the inguinal region and be inaccessible to observation. Nonetheless, the lower extremities should be systematically and frequently examined in all subjects with clinical settings which predispose to thrombosis and embolization.

The calves of the bed patient should be exam ned w th his knees flexed and with the feet resting comfortably in bed In this position the normal calf has a jellylike consistency Any localized resistance or tenderness should raise suspicion of underlying thrombophleb tis. In the ambulatory pat ent discon fort localized to the calf suggests thrombophleb tis. A centimeter or more of difference in the circumference of one calf over the other is a later sign as is p n on dorsiflex on of the foot. Enlargement of both thighs or a 1 5 cm difference n rcumference between the two measured 15 cm above the patella is suggestive of

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iliofemoral thrombophlebitis.[86] The physician should search carefully for venous dilatation on the soles of the feet and for pedal and ankle edema. He should also look for and palpate the saphenous and femoral veins. Tenderness or induration over these veins or inguinal lymphadenopathy is very suggestive of thrombophlebitis.

The recognition of venous thrombosis by ultrasound. Rushmer and associates[87] have recently described a new technique for evaluating the patency of peripheral blood vessels both arteries and veins, and for obtaining a qualitative estimate of the velocity of blood flow in the vessel. It is based on the principle that a sound wave reflected from a moving object undergoes an alteration in its pitch or frequency (the Doppler effect). The instrument which contains both the transmitting and receiving crystal is placed over the vessel so that the emitted sound wave (5 megacycles per second) is directed diagonally through the skin and subcutaneous tissues (Fig. 3). Stationary tissues will reflect the sound wave unaltered. Moving tissue (blood) will backscatter the beam at an altered frequency which is related to the velocity of blood flow. The unaltered reflected waves can be filtered out and the altered back scatter can be used to drive a loudspeaker. The acoustic characteristics of the sound so produced by normal arterial and venous flow are quite distinctive and readily recognized.[88] Sigel[89] and his associates have found the technique useful in detecting occult occlusion of veins in the lower extremity. They place the instrument head over the femoral vein. Pressure in a cephalad direction anywhere in the lower extremity will normally augment femoral vein blood velocity and increase the pitch of the reflected sound wave. They state that if a vein is occluded pressure distal to it will not result in normal augmentation. This technique is technically simple and harmless and the instrumentation is readily portable. If additional studies confirm its usefulness, the clinician will have available for the first time a sensitive objective diagnostic device for detecting a silent thrombotic process in the veins of the lower extremity. Whether the effects of collateral circulation will interfere with the diagnostic value of the test has not yet been determined.

Types of pulmonary embolism

Pulmonary embolism may be divided into (1) less-than massive and (2) massive. This distinction is obviously arbitrary but it has the merit of pinpointing the therapeutic problem. Massive pulmonary embolism is a therapeutic problem of the utmost urgency and its management requires a team of physicians. Less-than massive pulmonary embolism can frequently be taken care of by the attending physician himself. Massive pulmonary embolism refers to sudden complete occlusion of the right or left pulmonary artery or of

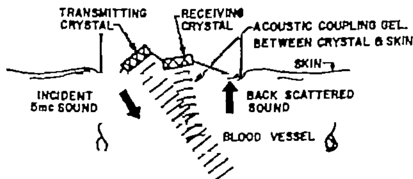


Fig. 3. Diagrammatic representation of the transmitting and receiving head of the ultrasound Doppler flowmeter. A sound wave (5 megacycles per second) is emitted by the transmitting head. It is reflected back by stationary tissues at the same frequency. Moving tissues (blood) backscatter the emitted sound wave at an altered frequency. The frequency of the backscattered wave is related to the velocity of blood flow from which it is reflected. (Reprinted through the courtesy of the authors and the publishers from Rushmer, R. F., Baker, D. W., Johnson, W. L., and Strandness, D. E., J.A.M.A. 199:326, 1967.)

both or of the main pulmonary artery or an occlusion which is superimposed upon pulmonary disease or previous embolization so that there is less than one third patency of the pulmonary circulation following the most recent onset. In about 15 per cent of patients the embolus contains a terminal appendage which extends through the pulmonary valve and dangles in the cavity of the right ventricle representing an additional potential cause for initiation of a fatal arrhythmia. Less-than-massive pulmonary embolism refers to embolization which occludes less than 60 per cent of the pulmonary circulation.

Less-than-massive pulmonary embolism. The symptoms of acute less-than massive pulmonary embolism are usually frustratingly nonspecific. This is so because the symptoms and signs are due to varying combinations of the effects, both local and systemic, of the embolus or emboli superimposed upon the local and systemic effects of the underlying predisposing disorder which is usually present.[10] Because the emboli differ considerably in size and number and because the underlying disorders are numerous the clinical picture is very variable. This variability accounts for the frequent failure to recognize the presence of pulmonary embolization. Indeed most pulmonary emboli are simply not recognizable on clinical grounds because they are too small to produce cardiorespiratory symptoms and the lung is devoid of pain fibers. Since only the parietal pleura has pain fibers, typical pleuritic pain can occur only when embolus is complicated by pulmonary infarction—which is uncommon. Even with infarction Gorham[12] found pleural pain in only 20 per cent of patients. It therefore follows that most instances of pulmonary emboli are clinically silent and that it is probable that subclinical pulmonary emboli may precede the first one clinically recognized. Indeed it has been estimated that as many as 90 per cent of pulmonary emboli are entirely silent. The diagnosis of pulmonary embolism will therefore be overlooked in at least 90 per cent of the cases if one suspects its presence only when classical findings of lower extremity thrombophlebitis are associated with a sudden onset of cough, pleuritic pain, and hemoptysis. Even hemoptysis, which is more frequent than pleuritic pain, is uncommon.

The most common symptoms are dyspnea, syncope, and palpitation; the commonest findings are fever and tachycardia.[10]

Dyspnea may be mistakenly attributed to a pulmonary infection or to exacerbation of underlying heart disease if this is present. Characteristically, the dyspnea is of abrupt onset and associated with hyperventilation with a feeling of anxiety. Rarely a patient may be aware that something has lodged in his chest even though pain is absent. Syncope is described by the patient as weakness or lightheadedness. Palpitation is also abrupt in onset and due to severe tachycardia or to atrial arrhythmia.

In the proper clinical setting pulmonary embolism should be suspected if there is a sudden rise in temperature associated with any one or combination of these symptoms. Recurrence of spikes of fever, of syncope, of paroxysmal atrial arrhythmias separately or together are particularly common manifestations, and are probably due to recurrent emboli which become suddenly impacted in the pulmonary circulation and subsequently fragment or dissolve.

The pulmonary lesions are frequently too small to be detected by physical examination. A pleural friction rub or signs of pleural effusion should bring to mind the possibility of embolism with infarction. Local wheezes and diffuse râles may be heard. If there is sufficient circulatory embarrassment, the second pulmonic sound may be accentuated and widely split. Clinical jaundice is occasionally present following an acute pulmonary embolus in patients with congestive heart failure.

Massive pulmonary embolism. The final common denominator of massive pulmonary embolism is occlusion of at least 60 per cent of the pulmonary arterial tree.[13, 14] For this reason the problem is primarily a mechanical obstructive hemodynamic one. This is particularly true if there is a single massive pulmonary embolus, but many of the other factors previously discussed may contribute to the syndrome if a smaller embolus is superimposed upon previous embolization.[13, 14]

Death may occur so suddenly that treatment and even medical attendance is not

possible If conscious, the patient is dyspneic or has a feeling of suffocation and this may be the only symptom probably because of mental obtundation Somnolence or coma with tachypnea may be the initial or terminal findings. If the patient is alert a feeling of impending doom and pain are frequently present

When present pain is characteristically of sudden onset constant severe, and retrosternal

The characteristic physical findings are those of right sided congestive heart failure associated with systemic hypotension One must however distinguish between two possible causes for systemic hypotension The impaction of an embolus in a major pulmonary artery may elicit a Bezold Jarisch type of reflex with hypotension and perhaps bradycardia and a slow respiratory rate [12] This reflex, however is transient lasting no more than 15 minutes. Prognosis during the first 15 minutes after the onset of a massive pulmonary embolus is difficult to evaluate because of this reflex hypotension and the tendency to spontaneous lysis If hypotension persists it is more likely to be due to mechanical occlusion of the pulmonary artery system and is an extremely ominous prognostic sign.

Tachypnea and tachycardia are present and cyanosis is common [12] Neck vein distention especially upon inspiration and a prominent A wave are commonly present A systolic murmur an accentuated and palpable second pulmonic sound which may be followed by a diastolic murmur a right sided gallop and systemic hypotension are all manifestations of the mechanical block in the pulmonary artery and acute failure of the right side of the heart [12] A pleuropericardial friction rub may be audible and on rare occasions an intrascapular bruit. According to Cobbs Logue and Dorney [14] the second sound may be widely split during expiration. This finding is attributed by them to shortening of left ventricular systole due to diminished stroke output and to prolongation of right ventricular systole due to the contraction of the weakened right ventricle against increased pulmonary resistance Coarse generalized inspiratory and expiratory wheezing are occasionally heard but more often physical examination of the lungs is not helpful

The history and physical findings may be strongly suggestive of acute massive pulmonary embolism but they are rarely pathognomonic. The differential diagnosis may include all other cardiac intrathoracic, vascular and pulmonary catastrophes—of which the most common is acute myocardial infarction

Roentgen manifestations

Conventional roentgen-ray studies may yield normal results even in acute massive pulmonary embolization and are hardly ever diagnostic by themselves, yet they are essential and frequently give clues which in conjunction with the clinical findings make pulmonary embolism the most likely diagnosis. Pulmonary embolism interferes with flow distal to the block. This hyperlucent region due to anemia or oligemia was first described by Westermark.[16] It is frequently overlooked because (1) one does not routinely attempt to follow the arterial branches to the periphery (2) the two-dimensional reproduction of the three-dimensional lung produces overlapping images of pulmonary vasculature and (3) increased bronchial flow may obscure the otherwise oligemic lung It is surprising however how often when looked for at least in retrospect the embolic portion of the lung appears hyperlucent compared to its nonembolic counterpart. If obstruction is sufficiently great and particularly when it is massive the right side of the heart and pulmonary artery and its major branches distend under pressure Perhaps because the right atrial border is more sharply defined in the posterior-anterior view and because the right atrium is more distensible increased convexity of the right atrial border and its extension to more than 50 mm beyond the midline is frequently the first change in the cardiac silhouette in our experience. [16] Other findings in succession are enlargement of the right pulmonary artery (>17 mm in males and >15 mm in females) enlargement of the pulmonary artery segment attenuation of the peripheral pulmonary branches and enlargement of the right ventricle which is best appreciated in the right anterior oblique view Dilatation of the superior vena cava and prominence of the azygos vein sign of venous hypertension and stasis, are oc



Fig 4 A Normal cardiovascular silhouette. B After m ssiv pulmonary embolus (necropsy confirmed) blocking the main pulmonary artery Note the oligemic lung fields, and the distention of the right trial border superior vena ca a, and azygos em The left border of the heart is formed by the right entricle hich is clearly abov the left leaf of the diaphragm

casionally seen (Fig 4) These findings, while subtle are more readily recognized if technically comparable films taken be fore the attack are available for comparison

Infarction of the lung is suggested by (1) elevation of a leaf (usually right) of the diaphragm with decreased excursion on fluoroscopy (2) blunting of the costo-phrenic angle and (3) a density (usually in the right lower lobe) with an overlying pleural effusion. [27] It is this pleural effusion which gives the infarct its hazy appearance and its ill-defined borders. Infarcts are located in the region of greatest pulmonary flow This is why the right lower lobe is the commonest and the left lower lobe the second commonest site of pulmonary infarc tion But when flow is abnormal (e.g in mitral stenosis) infarcts may be present elsewhere even in the apices of the lungs. Although less-than-massive pulmonary emboli are frequently multiple the infarct is more often solitary Roentgen evidence of infarction usually disappears quickly and completely (in days or a week) At times they are transformed into platelike atelectasis of variable length and direction. This variable direction is in contrast to the horizontal direction of linear atelectasis due to simple elevation of the leaf of the diaphragm Infarcts may remain for a long time as solitary nodules mimicking neoplasms or they may result in volume shrinkage of the lung These last two pictures are due to organi zation of hemorrhage and necrosis of complete infarction of the lung

Electrocardiographic changes

McGinn and White[16] were the first to describe the electrocardiographic findings of acute cor pulmonale The changes that appeared to them significant were an S wave and a slightly low origin of the T wave in Lead I a rather low origin of the T wave with a gradual sta rcase ascent of the ST segment interval in II a Q wave and the late inversion of the T wave in Lead III and a low or inverted T wave and an upright P wave in a right precordial lead The ST segment in III may be elevated They also stated that these changes come and go rather quickly with changes in the condition of the pat ent They attributed these changes to acute dilatation of the right ventricle Soon thereafter typical right bundle branch block was demon strated if the electrocardiogram was taken immediately after massive pulmonary em bolism [18]

McGinn and White stressed that these find ngs occur in only 10 per cent of patients because the obstruct on of the pulmonary circulation frequently is not of high enough degree. They also pointed out that ab-normal records due to pre-existing heart disease (especially coronary) may be fur tl er affected by the strain of the vascular

accident They concluded that a normal electrocardiogram is present in a large percentage of cases of pulmonary embolism but added that a slight degree of acute cor pulmonale or right axis deviation may be present.

Vectorcardiographic analysis suggests that the pattern of the acute cor pulmonale is due to an initial vector directed upward and to the left and a terminal one directed upward posteriorly and somewhat to the right. *The initial vector accounts for the* Q wave in Leads III and aVF and the terminal vector accounts for the S wave in I and sometimes in Lead II and III the R in the right precordial leads, and clockwise rotation of the electrical axis.[11,4]

Experience has confirmed McGinn and White's statement that a pattern of acute cor pulmonale is uncommon, transient (hours to a day or two) and occurs only with high grade pulmonary arterial obstruction. Our experience with lung scans indicates that pulmonary obstruction is almost always greater than that suggested by conventional films. It is therefore likely if electrocardiograms are taken early enough and repeatedly after a clinical episode which is subsequently found to be due to pulmonary embolism that electrocardiographic abnormalities may be present in a high proportion of cases. Indeed abnormalities have been reported from as high as 80 per cent in one series to as low as 20 per cent in another.[13] Because the electrocardiogram is a simple harmless bedside method of examination it should be used as the roentgen ray is to search for clues which together with the clinical picture can tip the scales toward the diagnosis of embolism and not simply to look for a characteristic pattern of acute cor pulmonale which is rare. The electrocardiographic changes are probably due to many factors acting in combination such as (1) acid base imbalance (2) hypoxia, (3) nervous stimulation and reflexes, (4) humoral secretions (5) pulmonary disease (6) elevation of the leaves of the diaphragm and (7) changes in character of respiration but the ones that are most obvious and supply more definitive clues for the diagnosis are (8) over *loading and ischemia of the right side of* the heart and (9) of the left side of the heart if it is the seat of independent (particularly coronary artery) disease. The following electrocardiographic abnormalities may be encountered in acute pulmonary embolism

Right atrial (1) Sinus tachycardia (2) right atrial preponderance (Fig 5) the initial portion of the P wave predominates and rotates to the right and anteriorly so that it may be taller than normal and the upright component in V_1 is predominant (more commonly the P waves are fused because of tachycardia, and right atrial preponderance is recognized by early peaking of the P wave these changes are usually associated with an auricular T wave) (3) atrial premature beats at times with aberrant ventricular conduction of the right bundle branch block (4) atrial tachycardia (5) atrial fibrillation and (6) atrial flutter

In the proper clinical setting transient and particularly recurrent episodes of these arrhythmias are strongly suggestive of the diagnosis of pulmonary embolism The evidence is especially strong if associated with the following ventricular changes (Fig 6)

Changes in the initial deflection of the

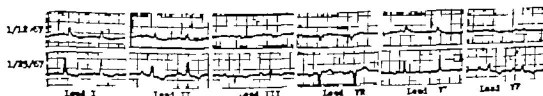


Fig 5 The tracing dated January 1 1967 was taken before the onset of acute symptoms; the one dated January 25 1967 was taken shortly after the onset of acute symptoms. Notice the appearance of the peaked and prominent right atrial P waves in Leads II III VL, and VF in the latter tracing

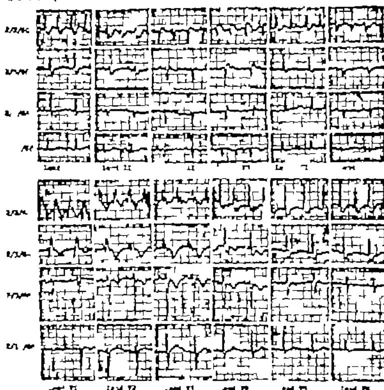


Fig. 6 The ECG changes of acute pulmonary embolism A supra entricular ta h ardia heralds the onset of acute pulmonary embolism Notice the S Lead I and II associated th Q I Lead III on the initial tracing of February 2 1966. The ST segment is also deeply depressed in Lead II The precordial leads taken that same dat show complete right bundle branch block associated th erted T wa es in the right precordial leads nd ST segment depression in the left precordial leads Serial tracings reveal gradual evolution of the pattern. By February 7 1966 the conduction defect had disappeared, revealing marked lockwise rotation in the precordial leads and deepl inverted T es in the right precordial leads The ECG of February 17 1966, as no longer abnormal.

QRS (1) Transient appearance of the classical pattern of right bundle branch block and or acute cor pul onale (2) abrupt right axis deviation beyond 90° (3) abrupt clockwise rotation (4) the abrupt appearance or increase in size of S and/or Q and (5) the abrupt appearance of a S pattern associated witl a q n \ These QRS changes are usually transient lasting hours to at the most sever l days.

Changes in the terminal deflection of the QRS (1) There may be abrupt inversion of the T waves in the right precordial leads. In contrast to the changes n in tial deflection, these changes may be early or late and may persist for weeks so a to be the only residual electrocardiographic evidence of pulmonary embolism These findings are frequently reported as coronary ischemia n the anteroseptal region by the electrocardiographer who is separated from the physician attending the patient Such isolated electrocardiographic find ngs should always lead the attending physician to search particularly in the history for evi dence of pulmonary embolism in the recent past

(2) There may be abrupt changes in ST T n the left precordial leads which may have the characteristic appearance associated with coronary ischemia (Fig 7)

Pulmonary embolism interferes with forward flow and may compromise the coronary circulation Furthermore pul monary embolism is common in the older patient who commonly has coronar artery disease which affects primaril

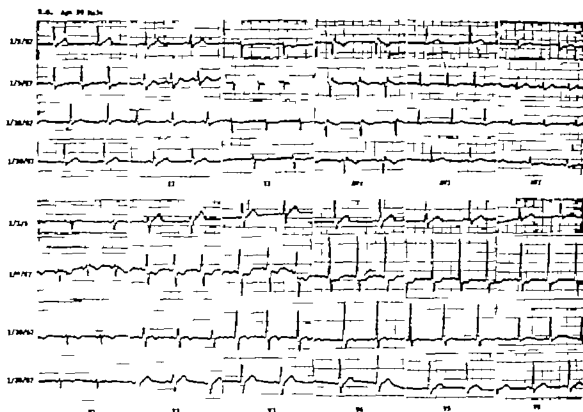


Fig. 7. Acute pulmonary embolism was recognized four days after spinal column fusion. Note the depressed ST segments in Lead I and II, the negative T waves in aVL, and the abnormal ST segments in the precordial leads taken on January 1, 1967. Note the return to normal tracing on January 20, 1967. Abnormalities over the left precordial leads had disappeared by January 15.

left ventricle. Pulmonary embolism may therefore further compromise coronary flow to the left ventricle and produce ST-T abnormalities characteristic of subendocardial ischemia. Indeed, in these patients who come to necropsy, subendocardial miliary necrosis of the left ventricle is a common finding.

Laboratory findings

The white cell count is usually less than 15,000 per cu. mm. and the proportion of neutrophilic leukocytes is not as great as is commonly seen in infection. Of greater diagnostic value is a triad first described by Wacker and his associates, elevated serum concentration of lactic dehydrogenase (LDH) and of bilirubin with a normal concentration of glutamic oxalacetic transaminase (SGOT). These observers emphasize that LDH concentration must be measured by a lactate-to-pyruvate spectrophotometric technique in order to avoid a high incidence of false-negative or false-positive results obtained by others using a colorimetric technique.[11]

We have not had a percentage of success (elevated concentration of LDH in 90 per cent and of bilirubin in 50 per cent of patients with acute embolism) reported by this group. In our experience hyperbilirubinemia in pulmonary infarction is uncommon unless congestive heart failure, infection, hepatic disease, renal failure, or shock are present. It is in these combinations that the SGOT is frequently elevated. Nevertheless, the triad, when present, is of differential diagnostic value. The LDH concentration usually rises, if it does at all, within 6 hours after the onset of symptoms and remains elevated for at least several days. More recently, this same group has reported excellent correlation between the results of LDH determination and those of lung scan.

Recently increased serum alkaline phos-

phatase activity has been reported one to three weeks after the onset of clinical symptoms of pulmonary infarction.

Determination of the carbon dioxide gradient between arterial blood and alveolar air and its limitations have already been discussed

Lung scanning

Scanning of the lung fields with a scintillation counter immediately after an intravenous injection of a gamma-emitting particle which cannot pass through the capillary bed is an excellent screening test for pulmonary embolism [133,135] The most commonly used material is macroaggregated human albumin labelled with I[131] The particle size should be between 15 and 20μ, and 95 per cent of these particles are normally trapped in the precapillary pulmonary arteriolar bed The usual dose administered contains up to 300 μc of I[131] which has a half life in the lung of 6 to 8 hours. The particles are handled by the reticuloendothelial cell and if the thyroid has been blocked by a prior administration of Lugol s solution over 80 per cent of the radioactivity can be recovered in the urine within 48 hours.[135] The procedure appears to be innocuous because only a very small fraction of the pulmonary capillary bed is occluded Studies in animals have demonstrated that these particles are distributed uniformly with the red blood cells in the pulmonary vasculature[133] The procedure has been improved technically by the use of fast moving scanners by simultaneous anterior and posterior scanning and by the addition of a blending device which facilitates visual evaluation of regional differences in density [133] With present techniques and limitation of resolution, an area of hypoperfusion must have a diameter of at least 3 cm to be detected on the lung scan

The technique has other limitations. Any parenchymal or pleural lesion is associated with hypoperfusion [133,134] The lung scan is therefore most helpful for detecting pulmonary emboli when conventional roentgen ray films show no evidence of pulmonary disease (Fig 8) [134] In such circumstances, avascular areas in the scan are presumably due to pulmonary embolism.

Because blood flow in the lung is not uniform—particularly in disease and with change in body position—the lung scan should be interpreted in conjunction with the chest film taken immediately before or after the scanning procedure (Figs 9 and 10) Furthermore the lung scan may be falsely positive in regions close to the external borders of the lung and adjacent to the heart particularly when the left ven-

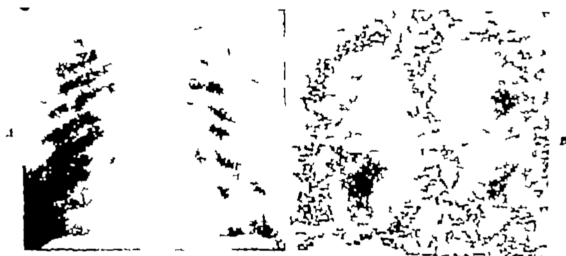


Fig 8 A P A roentgenogram of the chest of patient G P with recent pulmonary emboli Th film was interpreted as within normal limits B Lung scan of the same patient showing typical sickle-shaped area of hypoperfusion in the right midlung field and another area of hypoperfusion in the left lower lung field In retrospect ... of lung ... blood flow appear to be present in the routine chest film



Fig. 9. A, P.A. roentgenogram of the chest of patient D. C. The main pulmonary arteries are prominent and there is an area of equivocally increased translucency at the right apex. B, Lung scan of the same patient revealing several areas of hypoperfusion as a result of recurrent pulmonary emboli at the right apex, in the left mid lung field, and in the left lower lung field.



Fig. 10. A, P.A. roentgenogram of the chest of patient A. R. with recurrent pulmonary emboli. There is definite diminution in the pulmonary vascular markings to the left and right lung fields. B, Lung scan of the same patient showing many areas of hypoperfusion in both lung fields.

tricle is enlarged. The scan also fails to define the exact extent and location of the occluding emboli. This technique has promise of being a useful investigative tool in the study of such problems as the effect of heart and lung disease on the pulmonary blood flow, the regional flow response to pharmacologic agents, and the effect of thrombolytic therapy in the treatment of pulmonary embolism.[m]

Pulmonary angiography

Serial films taken following the pressure injection of 40 to 50 ml. of contrast substance into the right ventricle or main pulmonary artery will usually provide excellent definition of all of the lobar branches of the pulmonary arterial tree and fairly good definition of the segmental branches.[m,m] It will therefore establish the presence and extent of embolic occlusion within these vessels (Fig. 11A). The procedure also provides direct evidence of spontaneous or induced lysis of pulmonary emboli. The caliber of the main stem pulmonary artery varies between 20 and 30 mm. with an average of 26.4 mm.; that of the right main branch of the pulmonary artery varies



Fig. 11A. Pulmonary arteriogram obtained on patient M. S. suspected of having acute pulmonary embolism involving the main left pulmonary artery. The arteriogram confirms this impression and shows fairly normal filling of the right lung but a complete cutoff involving the left main pulmonary artery with little or no contrast material getting beyond this point. The opacification on the left side suggests previous pulmonary infarction and pleural effusion.



Fig. 11B. This patient was treated conservatively. Chest film obtained approximately 8 months later is similar to one taken one month later just before discharge of the patient from the hospital. The vascular markings in the left lung field appear to be normal and there is no enlargement of the left pulmonary artery. Although repeat arteriogram was not obtained on this patient, it appears likely that spontaneous lysis of the massive pulmonary embolus occurred. The raised left leaf of the diaphragm indicates volume loss of the lung and tends to confirm the impression of previous complete pulmonary infarct.

between 17 and 30 mm., with an average of 23.4 mm. A slight increase in caliber occurs with advancing age. Normally there is uniform and simultaneous filling and emptying of all areas of both lungs and fairly prompt opacification of the pulmonary venous system. A pulmonary embolus produces a sharp cutoff of contrast substance if the vessel is completely occluded (Fig. 11*B*) or a filling defect if the vessel is only partially occluded. A pulmonary angiogram may reveal regional delay in arterial inflow, diminished or delayed filling when compared with other areas in the lung. Such findings may be due to a pulmonary embolus but are also produced by abnormalities in flow due to pulmonary or cardiac disease.[130] Therefore angiocardiographically abnormal flow patterns should be interpreted only in conjunction with conventional roentgen film and with knowledge of the clinical problem.

The performance of a pulmonary arteriogram involves a small hazard to the patient, particularly if pulmonary hypertension is present.[131,132] The risk is slight but the procedure should not be requested without a reasonable diagnostic or therapeutic indication. The procedure also provides direct evidence of spontaneous or induced lysis of pulmonary emboli. The block may be replaced by an endothelial placquelike appearance or disappear entirely, giving rise to a normal arterial lumen. This procedure has given evidence that even very large emboli may be completely lysed within a few days or a week.[37] A pulmonary infarct may appear as an avascular region with associated volume loss.

Recent studies correlating lung scans with pulmonary angiograms have shown good agreement between the two techniques, but they should be considered complementary diagnostic tools, since each yields a different type of information.[131,133]

The recognition of a pulmonary embolus by ultrasound

Ultrasound techniques have recently been employed with considerable success in the diagnosis of both experimental and spontaneous pulmonary emboli.[34] If the underlying lung is normal, the sound wave is reflected from the thoracic wall and superficial layers of pulmonary tissue. In the presence of a pulmonary embolus

involved lung tissue is underperfused and the sound wave penetrates more deeply before it is reflected. The usefulness and limitations of this ingeniously simple and harmless technique have not as yet been demonstrated.

Prevention of pulmonary emboli

A prophylactic regimen is indicated for all persons with factors or clinical settings which predispose to the development of thrombophlebitis because pulmonary emboli, lethal or nonlethal, occur frequently without clinical evidence of their sources. The regimen includes the following: (1) The foot of the bed should be slightly elevated if practical. (2) The lower extremities should be exercised actively, if possible; if not, frequent passive motion is instituted. (3) Firm elastic stockings should be placed on both lower extremities up to the inguinal region. (4) Walking should be resumed as soon as possible. (5) Anticoagulant therapy is recommended provided no contraindication is present.

We are not impressed with statistical evidence which favors one method of anticoagulant treatment or one type of anticoagulant over another, provided adequate anticoagulation is achieved. We are prejudiced in favor of heparin for short term and oral anticoagulants for long term treatment.

We start with 10,000 to 15,000 units intravenously every four hours for the first 24 to 48 hours. Thereafter, the least amount is used which maintains a 2 to 2½ fold prolongation of the normal whole blood clotting time.[34] Treatment is continued until the patient is fully ambulatory. With effective anticoagulant prophylaxis, the incidence of phlebothrombosis and pulmonary embolism is very nearly zero. In a study of elderly patients with extremity fractures, the incidence of clinical thrombophlebitis in those not given prophylactic anticoagulants was 29 per cent; 18 per cent of these patients had a clinical pulmonary embolic episode, of which approximately half were fatal.[37]

Treatment of venous thrombosis

Treatment is identical with that outlined for prophylaxis. Walking is encouraged, if possible, after the first day of administration of anticoagulant therapy.

The anticoagulant of choice is heparin since the coumarin type of drugs do not produce an anticoagulant effect for two or more days and, in addition, they probably do not produce a significant in vivo antithrombotic effect during the first week of therapy.[19] The initial dose of heparin should be given intravenously and should not be less than 10,000 units (100 mg.). Some physicians prefer to maintain therapy with heparin administered intravenously at 4 to 6 hour intervals at a dose level sufficient to prolong the clotting time to 2 or 2½ times normal. Repeat venipunctures can be avoided by inserting a small capped indwelling needle. Others maintain anticoagulant therapy with heparin but choose to follow the initial intravenous dose with subcutaneously given concentrated heparin at 8 to 12 hour intervals.[33] Still others prefer to use a coumarin type of drug for maintenance therapy. Heparin should be administered for a full week to be certain that coumarin-induced antithrombotic activity has been achieved. The physician should keep in mind the fact that the Quick test may be an unreliable index of coumarin effect in a patient who is being given both heparin and a coumarin preparation.[34] Blood for the Quick test should be drawn just before a dose of heparin is to be administered rather than at a time when the blood level of heparin is higher. There is no substantial evidence to indicate that any one of these methods of treatment is superior to the other two. Some discontinue anticoagulant therapy after the patient is fully ambulatory, but one of us (L. A. S.) prefers to continue therapy for at least 2 to 4 months. He prescribes oral anticoagulants for the patients when they are discharged from the hospital.

Treatment of less than massive acute pulmonary embolism

Treatment is largely supportive.[38] It consists of the administration of oxygen, sedatives, and narcotics, the latter if the patient has severe pain. The intravenous infusion of isoproterenol (Isuprel) is indicated if the patient is seen very shortly after the onset of symptoms because this drug may diminish the transient generalized pulmonary arteriolar spasm and alveolar duct constriction which may contribute to the acute symptom. It may also be

helpful because of its inotropic and systemic vasopressor effects. Anticoagulant therapy should be instituted immediately with an intravenous dose of 10,000 to 15,000 units (100 to 150 mg.) of heparin to prevent further venous thrombosis and possible other effects. We prefer very large doses of heparin the first day, approximately 15,000 units (150 mg.) intravenously every 4 hours. If such large doses of heparin are given there is no need to measure the clotting time which is invariably greatly prolonged. The intramuscular administration of all medications should be avoided because of the risk of inducing a hematoma. One of us (L. A. S.) prefers to continue with intravenous heparin and switch to an oral anticoagulant several days before the patient is discharged from the hospital. The other (T. R.) prefers to initiate therapy with a single intravenous dose and then continue it with concentrated aqueous heparin subcutaneously at 6 to 8 hour intervals in doses sufficiently large to maintain the Lee-White clotting time greater than twice normal at all times. This usually requires approximately 400 mg. of heparin daily.

If the embolic episode can be clearly related to an acute problem such as surgery or trauma, anticoagulant therapy is continued for 3 months. If the underlying problem either is occult or due to chronic venous disease, anticoagulant therapy is continued for at least one year. The reason for the difference in treatment is that in the latter instances the risk of late recurrent pulmonary embolism and insidious development of pulmonary hypertension is distressingly more common. If there is evidence suggestive of recurrent pulmonary emboli or of pulmonary hypertension in these cases, anticoagulant therapy is continued indefinitely.

Experimental studies suggest that thrombolytic agents such as streptokinase and urokinase prevent thrombosis and accelerate [illegible]. It is hoped that such agents [illegible] reliable laboratory tests to control their use will become safe effective [illegible] available for clinical use.

In approximately 6 per cent of patients with pulmonary embolism surgical procedures to prevent recurrent embolic episodes [illegible] be necessary. The commonest indication for such a procedure are (1) recurrent pulmonary embolism in spite of apparent adequate anticoagulant therapy, (2) inability to maintain adequate anticoagulant therapy, and (3) contraindication to anticoagulant therapy such as a bleeding diathesis, the performance of recent surgery in an area from which hemorrhage is likely, or the need for several surgical procedures during a relatively short time.

If the clinical signs of thrombophlebitis have been limited to the legs, the procedure of choice is bilateral common femoral vein ligation. Long term edema and stasis are infrequently encountered following femoral vein ligation. The incidence of recurrent pulmonary embolism following this procedure is at least 10 per cent.

Surgery on the inferior vena cava is indicated for: (1) recurrent pulmonary emboli after femoral ligation, (2) evidence of venous thrombosis above the groin or recurrent pulmonary embolism following pelvic or rectal surgery not controlled by anticoagulants, (3) signs of venous thrombosis in the thigh with pulmonary embolism not controlled with anticoagulants, and (4) recurrent pulmonary embolism uncontrolled by anticoagulants in any patient with isolated left ventricular failure. The mortality from caval surgery is less than 5 per cent in patients free of heart disease but rises rapidly to 50 per cent in the presence of congestive heart failure. However, many of these latter patients probably would have died of their heart disease if surgery had not been done.

The surgeon has a choice of three procedures. The first is caval ligation. The disadvantages of this procedure are hypotension in the immediate postoperative period and at least a 10 per cent incidence of long term edema and stasis. Although some have stated that the incidence of recurrent pulmonary embolism following caval ligation is only a few per cent, others have suggested that the incidence of recurrence is at least 20 per cent as a result of the formation of large collateral vessels involving the lumbar veins (Fig. 12).

A second procedure that has been recommended is plication of the vena cava, which results in the production of many channels about 3 mm. in diameter. This procedure would appear to be contraindicated



Fig. 12. The development of large collaterals following inferior vena cava ligation. This bilateral venous angiogram taken several months after ligation of the inferior vena cava below the renal veins illustrates the development of very large collaterals by way of the lumbar venous system. These large collaterals are potential routes for large pulmonary emboli which may account for the 20 per cent incidence of recurrent pulmonary embolization following caval ligation reported by some observers. (Reprinted through the courtesy of the authors and the publishers from Gurewich, V., Thomas, D. P., and Rabinov, K. R.: New England J. Med. 274:1350, 1966.)

patients with multiple small recurrent emboli. The incidence of long-term edematous complications is said to be less than that following ligation provided thrombosis at the site of surgery does not occlude the vena cava completely. Unfortunately, complete caval occlusion does complicate this procedure in about two thirds of patients.[17]

The third procedure involves the insertion of mattress sutures in the vena cava to create a filterlike effect without narrowing the lumen of the vessel itself.[14] Experience with this procedure is limited. If it does effectively prevent recurrent large pulmonary emboli, it may turn out to be the procedure of choice since it is relatively free of long-term stasis and its complications and should not stimulate the development of large collateral routes of potential embolism. However, complete caval occlusion by thrombosis seems a likely possibility. These three procedures are illustrated in Fig. 13.

Regardless of what type of surgery is done, the need for long-term anticoagulant therapy frequently persists because of the underlying primary venous disease and the frequency of recurrences of pulmonary embolism. Indeed it is not clear from the statistics available on the recurrence rate after surgery that caval surgery has any advantage over anticoagulant therapy if such therapy can be effectively and safely provided.

Treatment of massive pulmonary embolism

Treatment is directed at supporting the circulation while preparing for possible surgery and using treatment outlined for less than massive acute pulmonary embolism.

No one so far as we know has sufficient experience to document the optimal treatment of massive pulmonary embolism. The following sequence seems reasonable:

1. Immediate institution of emergency conventional measures to treat hypoxia and to support circulation, namely, the administration of oxygen by mask or nasal catheter and of vasopressor inotropic agents, preferably by continuous intravenous infusion. We start with isoproterenol at a rate of 1 to 2 μg a minute. If systemic hypotension persists, norepinephrine at a rate of about 20 μg a minute and sodium bicarbonate or Tris buffer are given to combat the probable presence of lactic acidosis.

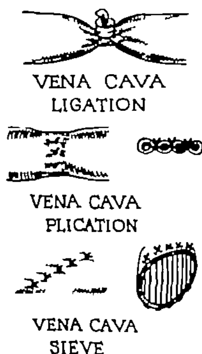


Fig. *13.* Diagrammatic illustration of surgical procedures on the inferior vena cava which have been advocated to prevent recurrent pulmonary embolism. The first is conventional ligation of the blood vessel. The second procedure is plication of the vena cava by use of mattress sutures which result in the production of a large number of channels approximately 3 mm. in diameter. The third and most recently recommended procedure is the production of a sievelike arrangement in the vena cava by use of mattress sutures without impingement on the cross-sectional area of the vessel itself. (Modified through courtesy of the author and the publishers from Bergan, J. J., Kinnaird, D. W., Koons, K., and Trippel, O. H.: Arch. Surg. 86:432, 1963.)

2. Immediate institution of anticoagulant therapy with intravenous heparin (at least 15,000 units or 150 mg. intravenously in a single dose).

3. Immediate administration of an antibiotic, a small dose of digitalis, and atropine sulfate to block vagal mediated reflexes. These measures are harmless and may be helpful and require no additional time.

4. Immediate request for bubble-type low prime oxygenator to be made ready for use at the patient's bedside.[43]

5. Immediate inscription of an electrocardiogram. If the tracing reveals clear-cut changes of an acute myocardial infarction and if there is no other compelling reason to suspect massive acute pulmonary embolism, the patient should be treated as one who has suffered a myocardial infarction.

6. Immediate withdrawal of blood for baseline enzyme studies, and acid base and electrolyte determinations.

7. By this time 15 minutes have elapsed and it is possible to establish whether the patient's hemodynamic status has improved. If the patient's status has improved and especially if there is no evidence of systemic hypotension, right ventricular failure, or other ominous signs such as an atrial arrhythmia, the patient's hemodynamic status should be monitored carefully. On the other hand if the patient's status has not improved or has deteriorated there is no time for delay since persistent hypotension, with or without signs of right ventricular failure, presages an imminent fatal outcome.[43,4]

8. Partial cardiopulmonary bypass between a femoral artery and femoral vein should be instituted with the standby pump oxygenator which requires no blood for priming. Once established this bypass will relieve the venous congestion and improve the systemic and coronary circulation whether the diagnosis is massive acute pulmonary embolism or some other catastrophe. This procedure carries with it only the small theoretical risk of dislodging other thrombi in the iliofemoral venous system.

9. Immediate pulmonary arteriogram. Lung scans are difficult to interpret with confidence in the absence of conventional roentgenograms. This is particularly true when pulmonary blood flow is abnormal, which is frequently the case in a person with circulatory collapse and possibly with an underlying cardiac disorder. Satisfactory lung scans are also difficult to obtain in patients who are critically ill, who are dyspneic, and who have irregular respirations. Therefore we bypass lung scanning and accept the minimal risk of pulmonary angiography. Indeed if the situation is an unusually critical one, the story clearly that of previous less-than-massive pulmonary embolism and thrombophlebitis, and if the electrocardiogram is diagnostic of acute cor pulmonale, we would be willing to bypass even the pulmonary angiogram and proceed immediately to operation. Such instances are very rare. The pulmonary arteriogram will nearly always delineate the location and extent of the embolic occlusion. A direct cur

defibrillator should be available to treat any potentially lethal arrhythmia.

10. If the pulmonary angiogram confirms the diagnosis of massive acute pulmonary embolism the patient should be taken immediately to the operating room (if he is not already there). Operation is preferably done with the patient on complete cardiopulmonary bypass. Some surgeons continue to use the conventional Trendelenburg technique[148] or a sternotomy approach.[31,150] All surgeons agree that the inferior vena cava should be ligated just below the renal veins after pulmonary embolectomy. During the postoperative period metabolic acidosis may occur and should be treated with alkalis such as sodium bicarbonate or Tris buffer.

It has already been mentioned that some investigators believe that acute massive pulmonary embolism may be evaluated by measurement of the right ventricular pressure following insertion into the right ventricle of a flow guided catheter at the bedside.[27] A mean pressure of less than 30 cm H_2O (22 mm Hg) is said to justify conservative management while a pressure above 30 cm H_2O indicates the need for embolectomy if the patient's life is to be saved. This procedure may frequently be quite time consuming. It does not make a morphologic or etiologic diagnosis, since it reflects an elevation of right ventricular diastolic pressure which may result from a multitude of causes. In addition, others have reported survival of over 50 per cent of patients with mean pressures above 30 cm H_2O.[133]

One may reasonably wonder how many patients may be saved by this complex regimen which requires much equipment and a trained team. In Fig. 14 we have plotted the survival time of patients with massive acute pulmonary embolism from the onset of symptoms to death based on data available in the literature.[23,131,78] Sixty per cent of patients are dead within 30 minutes from the onset of symptoms, the minimal possible time required to institute partial cardiopulmonary bypass, a potentially life-prolonging procedure.[131,134] Therefore even under the most ideal circumstances, only 40 per cent of such patients can be saved by currently available techniques. Gifford and Groves[137] recently reviewed a decade of experience with mas-

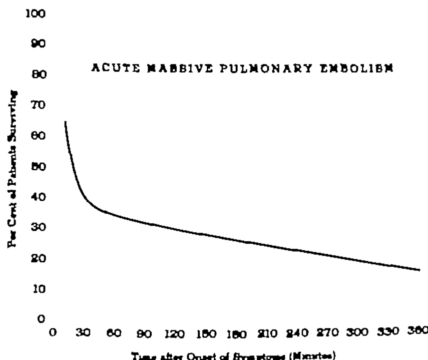


Fig. 14. Graphic representation of the survival time of patients with acute massive pulmonary embolism from the onset of symptoms. Only 40 per cent of patients survived 30 minutes, the minimal time required to [illegible]tute partial cardiopulmonary bypass.

sive acute pulmonary embolism in the Cleveland Clinic. Their analysis suggests a rather pessimistic outlook. The clinical picture of an acute hemodynamic catastrophe was absent in about one fourth of their patients, thus reducing the maximal salvageable group to 30 per cent. In addition, intractable heart failure, severe infection, uncontrolled cancer, recent myocardial infarction, and massive cerebral infarction were present in many of their patients. They found that only 11 per cent of patients with massive acute embolus survived 30 minutes and were acceptable risks for surgery. This group constituted 9 patients encountered at a large medical center during a 10 year period or about one potentially salvageable patient a year. Their study did reveal a high incidence of massive pulmonary embolus postoperatively in patients who had undergone vascular surgery. An energetic approach to this problem may therefore be justified in centers in which a great deal of this type of surgery is performed.

This report of Gifford and Groves, which is similar to an analysis of our own cases, is in sharp contrast to reports appearing recently from surgical clinics. Thus one group reports the occurrence of five cases of massive pulmonary embolism within a short time with three survivors,[166] and another twelve cases with four survivors,[14] and a third 10 cases with only three operative deaths.[166] The reason for this discrepancy is not clear, but the following points may be pertinent.

Clinical acute pulmonary embolism is primarily a physiologic diagnosis, whereas the necropsy diagnosis of massive pulmonary embolism is primarily anatomic. Multiple small pulmonary emboli engrafted upon previously diseased lungs may produce the clinical picture of acute massive pulmonary embolism but may be misinterpreted by the pathologist as less-than-massive. On the other hand, the enthusiastic clinician leans toward the diagnosis of massive pulmonary embolism when indeed the problem is that of less-than-massive. Even massive pulmonary emboli tend to lyse spontaneously and it is this knowledge, plus the self-limiting Bezold-Jarisch reflex, which makes the clinician willing to wait for 15 to 30 minutes after the institution of energetic medical therapy before considering surgery.[2] Such lysis may continue after death, so that many clinical cases of massive pulmonary embolism may not appear massive at the time of necropsy. Gifford and Groves's study was a retrospective one, whereas the surgical reports deal with living patients. Finally, it is not possible at all times to determine the surgical findings at necropsy because the surgical maneuvers and those of the anesthetist may have removed or dislodged all or parts of the thrombus (or thrombi) without saving the life of the patient.

It would appear likely that the true incidence of acute massive pulmonary embolus, whether due to a large thrombus in the main pulmonary artery or to multiple small emboli in peripheral arteries, is higher than that found at necropsy. Therefore, we believe that an effective team for performing pulmonary embolectomy should be available, particularly in those institutions which admit a large number of patients with disorders having a high incidence of complicating thrombophlebitis and acute pulmonary embolism.

Finally, it is worth re-emphasizing that the best hope of reducing the mortality from acute massive pulmonary embolism lies not in treatment but in prevention, and that lethal pulmonary emboli are frequently preceded by smaller ones.[11, 41] Barker and co-workers[34] found that, if a patient had a pulmonary embolism after operation and survived, there is a 43.8 per cent chance of another thrombotic episode, a 30.5 per cent chance of another embolism, and an 18.3 per cent chance of a fatal embolism in the same postoperative convalescence.[34] It is hoped that a safe effective thrombolytic agent will soon be available which, with or without partial cardiopulmonary bypass, will dissolve pulmonary and other thrombi and thus make pulmonary embolectomy of only historic interest.

Summary

Pulmonary embolism is the commonest lethal pulmonary disease in the United States and is a contributing cause to the deaths of many additional patients. Yet its clinical recognition remains difficult and often impossible. This is so because the lung has no pain fibers, and has a large v

reserve and because clinical manifestations, when present are variable complex and not infrequently completely obscured by the underlying disorder It is unlikely that additional clinical observations will significantly increase accuracy of diagnosis. Increased accuracy of diagnosis will depend upon the development of new screening tests and the fullest use of those presently available These latter are the triad of increased serum lactic dehydrogenase and bilirubin with a normal serum glutamic oxalacetic transaminase frequently repeated electrocardiograms and roentgenograms of the chest lung scanning and (hopefully) ultrasound There would appear to be no reason to use screening tests in the vast majority of instances of pulmonary embolism which are clinically silent and free of clinical precursors, and yet these emboli may be forerunners of an additional pulmonary embolism for which treatment is still not satisfactory Hence the best hope for reducing the morbidity and mortality from pulmonary emboli lies not in treatment but in prevention

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

The treatment of cardiogenic shock

III. The use of isoproterenol in cardiogenic shock

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The β-adrenergic stimulant actions of isoproterenol suggest that this drug should be beneficial in countering the cardiodynamic and hemodynamic abnormalities of cardiogenic shock. The present discussion is limited to the shock accompanying acute myocardial infarction and excludes the shock primarily due to cardiac arrhythmias, chronic heart failure, and cardiac toxins.

Hemodynamic considerations

General consensus holds that the shock of myocardial infarction is due to a primary failure of contractility of the heart muscle and hence a primary failure of the ability of the ventricle to expel blood. Several disturbing facts make this assumption still unproved: thus, the occurrence of shock has not been satisfactorily related to the size or location of the infarcted heart muscle; large fibrotic infarcted areas of myocardium are found at autopsy of patients who did not have shock; cardiac output has been found normal in some patients with typical myocardial infarction shock. It is conceivable but neither proved nor disproved that the shock in myocardial infarction may result from some other mechanism.

The present discussion assumes that the shock in myocardial infarction results from a primary power failure of the cardiac pump to expel an adequate amount of blood. In an attempt to maintain systemic blood pressure generalized vasoconstriction occurs and involves arterioles, arteries, veins, and cardiac chambers. Nevertheless, blood pressure falls, but may be maintained or even rise. Reduced organ blood flow persists. Shock exists when organ blood flow falls below a critical level regardless of what the blood pressure may be. Shock is a failure of blood flow, not a failure of blood pressure. Shock is a low flow, high vascular resistance state in which pulse pressure is small and systemic blood pressure usually reduced. Helpful guides to the failure of blood flow are small pulse pressure (poor stroke output), wet cold skin, restlessness or torpor, air hunger, tachycardia, and poor urine output.

Consequent to the decreased organ blood flow, secondary abnormalities develop which are deleterious in themselves, and which may adversely affect myocardial function. Decreased venous return induces tachycardia, which of itself increases myocardial oxygen and substrates needs. Tissue hypoxia leads to acidosis. Increased capillary permeability reduces blood volume, further decreases venous return, and renders the blood more viscid and less flowable. Glomerular filtration falls and oliguria or anuria develop. Poor cerebral blood flow leads to restlessness or torpor.

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and faulty function of the sympathetic nervous system

Cardiodynamic considerations

The function of the heart as a pump now failing is dependent upon the function of the heart muscle cells and their aggregate the myocardial fiber The focus should be first on the heart as a muscle and secondarily as a pump The function of the myocardial fiber is no different from the function of the skeletal muscle fiber—to produce shortening and contraction This result is produced by increase in tension within the muscle cells The function of the myocardial muscle fiber is concerned only with the tension produced and the degree and rate of fiber shortening not with the blood expelled from the ventricular cavity It is only an anatomical happenstance that the contracting heart muscle fibers expel blood albeit an important physiological happenstance for organ function depends on that blood and we live as a result of the summated function of our organs. The point is repeated that more attention must be focused on the heart as a muscle, and a cell to understand the function of the heart as a pump This concept is important in shock where therapy directed toward increasing blood pressure or improving cardiac output may impose an undesirable and unbearable stress on the heart muscle

The function of the heart muscle cell and thus of the myocardial fiber and the heart will depend on the supply of substrate and oxygen The uptake of oxygen the utilization of substrate and the turnover of high energy donors (creatine phosphate and ATP) is directly related to the tension produced by the cardiac muscle fiber and the rate of production of that tension Thus, the tension the fiber for the time the tension is maintained (approximated by the pressure in the left ventricle multiplied by time) and the rate of development of that tension (measured by rate of fiber shortening) determine the heart need for oxygen high energy donors, and substrate In terms of the circulation the stress on the heart (its internal work and its need for oxygen energy donors, and substrate) is increased when the blood pressure rises for the heart muscle must develop more tension to expel blood when the ventricle builds up pressure more rapidly to expel the blood for fiber shortening rate is greater and when the frequency of contraction increases, tachycardia

In the shock state the load on the heart is decreased by the lowered systemic blood pressure but increased by the tachycardia and by the rapidity of contraction of the relatively empty ventricle Whatever the energy cost to the heart the resulting cardiac output is not adequate for organ function and thus not for patient survival Agents which solely increase systemic blood pressure are undesirable for they simply increase the tension and load which the failing heart muscle must develop Moreover when such agents increase systemic blood pressure by generalized vasoconstriction there is no assurance that organ blood flow will be increased even though the blood pressure is raised Indeed organ blood flow may decrease because increased vascular resistance may outweigh the increase in blood pressure The result can be altogether bad the failing heart muscle is required to do more internal work (produce increased tension) the increased need for energy donors and oxygen may not be met because coronary blood flow may not increase proportionately and unfortunately the organ blood flow (cardiac output) may not be increased

A desirable agent for treatment of myocardial infarction shock would have two effects release the systemic vasoconstriction and supply inotropic stimulus to the failing heart muscle Isoproterenol has these two actions

By releasing systemic vascular resistance organ blood flow should increase even at lowered arterial pressures. Venous return would increase and tachycardia decrease The increased cardiac output would be expected to maintain mean arterial blood pressure in the presence of general vasodilatation These several effects would decrease the load (energy requirement) on the heart muscle and still secure better organ blood flow Supplying inotropic catecholamines seems logical since patients with myocardial infarction have ischemic heart disease and inotropic catecholamine content of the heart muscle is probably already

decreased (decreases have been demonstrated in patients with this type of heart disease when in congestive heart failure)

Pharmacological actions of isoproterenol

Isoproterenol stimulates β-adrenergic receptors. In animal experiments, the drug has the following effects (1) on the heart increased ventricular systolic force increased ventricular rate increased myocardial oxygen consumption these effects of themselves would be undesirable in shock but note that an inotrope is being supplied (2) on the coronary artery direct vasodilatation with increased coronary blood flow due to decreased coronary vascular resistance[3] this effect would permit increased supply of required energy donors for the greater direct inotropic action and (3) on the systemic circulation widespread dilatation of blood vessels, certainly of skeletal muscle and perhaps also of the skin and gut decreases systemic vascular resistance[3] in shock this effect permits greater organ blood flow at a lower systemic pressure. Isoproterenol is also a good bronchodilator—a desirable effect in shock permitting better pulmonary ventilation in face of bronchoconstriction and pulmonary congestion

Isoproterenol produces similar effects in man both in persons without heart disease and in patients with valvular and ischemic heart disease (1) The cardiac effects are increase in cardiac output index and stroke index, slight increase in pressure time index (tension) due to increase in ventricular rate since pressure time (tension) per beat decreased increase in left ventricular ejection rate due to a more rapid rate of myocardial fiber shortening decrease in left ventricular mean volume through more effective emptying of the ventricle producing also a small decrease in left ventricular end diastolic volume and pressure and increase in myocardial oxygen uptake out of proportion to the pressure time (tension) index probably due to the increased rate of fiber shortening (2) The coronary artery effects include a decided increase in coronary blood flow due to a marked decrease in coronary vascular resistance Moreover since the oxygen content of coronary sinus blood rose, the increase in coronary blood flow exceeded the increase in myocardial demands. Accordingly myocardial aerobic efficiency did not change and no anaerobic myocardial metabolism developed even though myocardial work was greater The effect on the coronary artery circulation represented primary and secondary vasodilatation (3) The main hemodynamic effect is a markedly decreased systemic vascular resistance indicating a general vascular dilatation Cardiac output increased to compensate and maintain systolic diastolic and mean blood pressures at slightly lower levels. Total body metabolism as determined by oxygen consumption increased

Clinical experience

Because of its myocardial inotropic action its systemic vasodilator action, and importantly its coronary dilator effect, which permitted the increased inotropism and increased systemic blood flow to be borne without reduction in myocardial efficiency isoproterenol seemed like a good drug to use in cardiogenic shock. There is always the question whether results obtained in animals apply to man with disease states and whether effects in man in non-shock states, including heart disease apply to the shock state in man Isoproterenol has been reported to have beneficial effects in both hemorrhagic shock and endotoxin shock in animals[4,5] and in man.

Isoproterenol has been used as the basic drug in the treatment of the shock of myocardial infarction in this large municipal hospital. Because the drug is vasodilator and because patients in shock have low blood volumes, blood volume expansion was used concomitantly with the isoproterenol. The results thus far have been equivocal but perhaps hopeful.

Most patients were in severe shock and elderly and had in addition other disease states. Conventional treatment measures were always instituted without delay and included when needed acute resuscitative measures, morphine oxygen assisted respiration by mechanical apparatus, digitalis preparations lidocaine or Pronestyl mannitol steroids, and alkali A catheter placed in the superior vena cava monitored

central venous pressure The usual electrocardiograph monitor defibrillator was attached

Blood was preferred for blood volume expansion and 1 to 5 units in 24 hours were given. Dextran was occasionally used while waiting for blood. Isoproterenol was given as a drip intravenous infusion in 5 per cent dextrose in water The starting rate was 2 μg per minute and altered as necessary The highest infusion rate was 12 μg per minute. The longest duration of isoproterenol infusion was five days.

A total of 26 patients were treated in this manner 7 recovered from shock 19 did not

The most common result was persistence of hypotension (systolic pressure below 100 mm Hg) and clinical evidence of low organ blood flow restlessness or torpor tachycardia, cool wet skin oliguria rising central venous pressure (15 to 20 cm H_2O) and death in less than 12 hours (one patient 34 hours) The 11 patients in this category were 46 to 78 years old (average 67 years) The isoproterenol infusion rate ranged from 1 to 8 μg per minute (average 2 5 μg per minute) and the duration of infusion from 1 to 34 hours (average 9 hours)

Eight patients, ages 46 to 82 years (average 67 years) improved temporarily in spite of equally low blood pressures and became clearer mentally the skin became dry but often remained cool tachycardia decreased urine was formed at a reduced rate, 5 to 15 ml. per hour (perhaps mannitol induced) The improved state was not maintained After several hours to several days, the circulation lapsed gradually into a full shock state and after variable periods the patient died The isoproterenol infusion rate ranged from 1 to 12 μg per minute (average 3.2 μg per minute) and the duration of infusion from 9 to 123 hours (average 40½ hours)

In the seven patients, ages 51 to 73 years (average 61 years) who recovered from shock blood pressure remained equally low and was maintained for variable hours to days with the patient slowly becoming more lucid and cooperative the skin drying but cool the tachycardia decreasing, and urine flow maintained at low levels, 10 to 20 ml. per hour After 4 to 64 hours (average 21 8 hours) it was possible to discontinue the isoproterenol infusion the rates had been 1 to 8 μg per minute (average 7 6 μg per minute) For several days thereafter a low blood pressure state with decreased but not inadequate organ blood flow was evident and maintained without specific therapy Gradually the patient recovered It was characteristic of these patients that the blood pressure remained low even at "shock" levels. Four of the seven patients died 2 2½ 4 and 6 days after isoproterenol was discontinued and the shock state seemingly corrected

Several impressions remain at this time Isoproterenol did not "drop the bottom" out of the blood pressure with catastrophe to the patient The patients certainly did no worse than similar patients receiving vasopressor drugs.[8] They looked somewhat better at comparably low blood pressures. Isoproterenol did not induce aberrant ventricular activity at the usual dose of 2 μg per minute At higher doses, greater than 6 μg per minute ventricular aberrant activity did at times, occur Reduction of infusion rates or administration of antiarrhythmic drugs controlled the aberrant activity The shock state plus transfusion of blood raised central venous pressure to levels considered undesirable (18 to 20 cm H_2O) but without pulmonary edema. Death often sudden after a considerable satisfactory period leaves open the question whether the increased inotropic effect and increased myocardial oxygen requiring effects of the drug led to demands exceeding their supply

One can postulate that the occurrence of shock in myocardial infarction and recovery therefrom is related to the degree of sclerosis of the coronary arteries of the noninfarcted heart muscle and hence to the blood flow in the noninfarcted muscle. Thus, when these arteries are not involved or only slightly so shock would not occur or if it does, recovery could be brought about by appropriate treatment On the other hand when these coronary arteries are much sclerosed the circulation to the noninfarcted myocardium would fall below the requirements of this heart muscle to maintain the work required to sustain

the general circulation. Shock would then ensue. Similarly, the failure of recovery from shock during the action of isoproterenol could be due to the failure of blood flow through the obstructing coronary arteries to noninfarcted muscle to increase proportionately to the increased myocardial metabolism induced by the isoproterenol. The coronary circulation would then not keep pace with the increased metabolic activity; the heart muscle would have to undergo anaerobic metabolism and would subsequently fail. At any rate, it has been established in patients with coronary atherosclerosis that areas of myocardium supplied by sclerotic coronary arteries produce lactic acid (evidence of anaerobic metabolism) during the infusion of isoproterenol, whereas in the same heart no lactic acid is produced by areas with uninvolved or minimally involved coronary arteries or with adequate collateral blood supply when the coronary sclerosis is severe.

Finally, a new approach is demanded by any illness which has a mortality rate of 75 to 95 per cent, as myocardial infarction shock does with current modes of therapy. The patient should be moved into a unit where a skilled team, using modern methods based on cardiac catheterization and hemodynamic techniques, will measure, hour by hour, basic cardiac, circulatory, and metabolic functions. Guided by such information, proper use can be made, as individually needed, of the effective α- and β-adrenergic stimulant and blocking drugs, volume expanders, and inotropic agents which are available today.

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Annotations

Conversion of atrial flutter to sinus rhythm after stimulation of carotid sinus

In patients with atrial flutter stimulation of the carotid sinus usually increases the degree of A-V block and slows the ventricular rate. The fact that the rate and form of the atrial-flutter waves are ordinarily unaffected facilitates the diagnosis. Sinus rhythm is rarely restored after carotid-sinus stimulation. The present report will document the conversion of atrial flutter to a sinus mechanism by carotid-sinus stimulation.

A 67-year-old man was in good health until August 1965 when he was admitted to a hospital in New York City because of persistent cough and weight loss of 4 pounds. A chest x-ray revealed a large, left hilar mass with collapse of the left upper lobe. Subsequent bronchoscopy indicated a bronchogenic carcinoma. The patient was then transferred to the Bronx Veterans Administration Hospital for radiation treatment of the neoplasm. The past history, careful physical examination and chest roentgenogram did not reveal evidence of heart disease. The blood pressure was 120/90, the temperature was 98° F, and the pulse was 150 and regular. Dullness and diminished breath sounds were audible over the upper half of the left hemithorax.

An ECG showed atrial flutter at a rate of 300 per minute and a ventricular rate of 150. The QRS complexes were within normal limits. A complete blood count, urinalyses, and tests of renal function were within normal limits.

Stimulation of the right carotid sinus under continuous electrocardiographic monitoring led to an immediate slowing of the ventricular rate due to the establishment of a regular sinus rhythm, but this was of brief duration and atrial flutter then recurred. Restimulation of the carotid sinus again produced sinus rhythm, and this time it persisted (Fig. 1).

Carotid-sinus pressure is of value in the differential diagnosis and treatment of atrial arrhythmias. Carotid-sinus stimulation will usually either terminate or not effect paroxysmal atrial tachycardia or paroxysmal A-V nodal tachycardia. Atrial flutter may be slightly and temporarily slowed by carotid-sinus pressure or there may be a sharp reduction in ventricular rate. Sinus rhythm is not restored as it is in atrial tachycardia.

But, contrary to wide belief, these rules are not absolute. Bellet observed three patients who had received digitalis and in whom carotid-sinus pressure was effective in converting atrial flutter to atrial fibrillation. In one previously reported case, carotid-sinus massage terminated an attack of atrial flutter and restored sinus rhythm. Recently, Hilal and Massumi[2] reported that in a patient with atrial flutter carotid-sinus stimulation led to fatal ventricular fibrillation.

In our patient we were twice able to restore sinus rhythm by pressure applied to the carotid sinus. This virtually eliminated the possibility

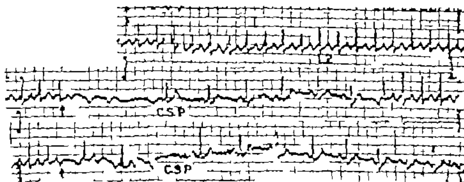


Fig. 1. Sequential strips of Lead II taken before, during, and after two carotid-sinus stimulations. In the top strip note the presence of atrial flutter with 2:1 A-V block. In the middle strip two premature ventricular contractions are followed by transient sinus rhythm. Atrial flutter then recurs. In the lower strip, carotid-sinus pressure again produces two premature ventricular contractions which are followed by persistent sinus rhythm.

that this con ersion was ponta eou and unre lated t carot d-sin timulation

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Methysergide and coronary artery disease

The effecti prophylactic treatment of migraine prese ted manifold difficulties for many years and the hronic incapacity of patient subject t re rrent severe tta ks and the difficulties experienced in their management were well known. The dangers of prolonged use of ergot alkaloids ha been documented by Von Storch od the recent ggest on that oral progestational agents may be sef P has not been borne out by the results of controlled cross-over trial. O the basis of several studies, -7 methysergide (Sandoz) ppears t be the most effect gent llable at present for th prophylaxis of migraine The minor side effects of this drug (na sea, ertigo muscle pai and cramps) are usuall transient although I some ases they may necessitat its withdraw l. A number of reports ha associated methysergide therapy w th retroperitoneal fibrosis 10 I these cases the retroperitoneal fibros regressed after withdrawal of the drug although L tz and sociates felt that a direct cause-and-effect relationship had not been established their patients In nother report Schwart od D nea[11] described patient i whom retroperitoneal fibrosis f llowed methysergide ther py od did not regress fter withdrawal of the drug Apart from this, methysergide has not been implicated in the causation of serious illness. I particular there has been no suggestion that it might precipitat cardiac infarction i pparently healthy subjects. A recent review of the literature[12] showed that, in some 9,000 patients who had taken methysergide, only 4 cases of cardiac infarction od 16 cases of angina pectoris were recorded I spit of this, the manufacturers ad se against its use in patients know t be suffering from coronary rtery disease and *Lancet*[13] warned that angina may be a side effect. Furthermore a patient suffering from retroperitoneal fibrosis ssociated with methysergide therapy report d by Carr and Biswas[14] was also in cardiac fail re although he was nor motens (blood pressure 150/80) and umber of the patient described by Graham od colleagues dev loped nexplained cardiac murmurs while taking the drug I recent report however Hudgson and co-workers described three cases of cardiac i farction (one f tal) and one case of acute coronary nsufficiency in middle-aged migrainous subjects who were on long-term methysergide prophylaxis. None of these patients had previously displayed any symptom suggesting coronary-artery disease I the first case f tal cardiac i farction occurred one month after commencing methysergide 2 mg twice daily I the other three the onset of symptoms occurred 6 7 and 11 months, respectively after treatment had commenced All three were taking methysergid 2 mg three times day The fourth patient, 42 year-old man had been given Cafergot tablets to be taken as necessary for his attacks but he had not taken any for four months prior t his cardiac infarct. H has since had frequent ttacks of transient monocular blindness and cerebral schemia affecting both the right od left hemispheres. Panarteriography showed widespread and severe therosclerotic degeneration i the intracranial essels, and he is now receiving long term anticoagulant therapy

The authors believ that, while the association could well be coincidental, it is difficult to escape the conclusion that the drug may ha been responsible for precipitating ttacks of myocardial ischemia in th four patients described W now exercise extreme ca tion i prescribing methysergide in those patients ho might reasonably be suspected of ha ing silent coronary-artery disease, nd w employ ll possible lternatives first In fact, we now mak practice of recording an electroc rdiogram fter exertion in all patients ver the age of 40 in whom the use of methysergide is contemplated

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A new display in vectorcardiography*

Some years ago we proposed a sphere as a frame of reference for 3 dimensional vectorcardiographic forces. On this sphere, longitude is measured from the left and ranges from 0° to 180°. The anterior hemisphere is positive and the posterior is negative. Latitude ranges from 0° to 90°. The inferior hemisphere is positive and the superior is negative.

A vector arising at the center of the sphere, pierces its surface at a point and is represented at that point by a small, round spot whose area is proportionate to the magnitude of the vector. The instantaneous forces of a vector loop are displayed by a sweep of such spots across the face of the sphere: this sweep tracks the course of the loop in space. An example is shown in Fig. 1, A, a normal subject whose projections and orthogonal leads are given in B and E. This was prepared by hand. The instantaneous vectors were determined by rectal (sic) of horizontal projecting plane geometric technique that had used for the determination of the ventricular gradient. They were then appropriately positioned on the sphere and photographed. It is now possible to draw a more effective display by electronic means.

The Stromberg-Carlson 4020 computer-recorder converts computer data into points and lines on the face of a specialized cathode ray tube. It is equipped with a still camera and motion picture camera that record onto microfilm and paper and, because it follows programmed instructions, it is capable of prodigious feats of draftsmanship at electronic speed.

For our purposes, the instructions are as follows: given the successive Cartesian coordinates of a loop in space, draw the loop on a fixed frame of reference as seen by an observer on a given axis at a given distance, and do this in accordance with the rules of perspective. Specific information such as the observer axis in terms of longitude and latitude, the distance of the observer from the center of the sphere, the radius of the sphere and timing intervals, etc. is also provided.

The orthogonal components of our subject, as derived by the Frank system, were simultaneously recorded on magnetic tape. This was converted to digital form by an analog-digital converter and passed through a programmed IBM 7094 digital computer which reduced the data to a format compatible with the SC 4020, which then drew and photographed the pictures on paper. The entire procedure is tape-to-tape and the same program is used for all subjects.

Fig. 1, C was drawn by the SC 4020. The sphere is graticulated at 30° intervals. The X axis is included to orient the reader. Its positive pole is marked by a solid circle and its negative pole is marked by an open circle. This is a temporary expedient and these symbols are not drawn

*Supported by Grant 5 RO1 HE09987-02 from the National Heart Institute of the United States Public Health Service.

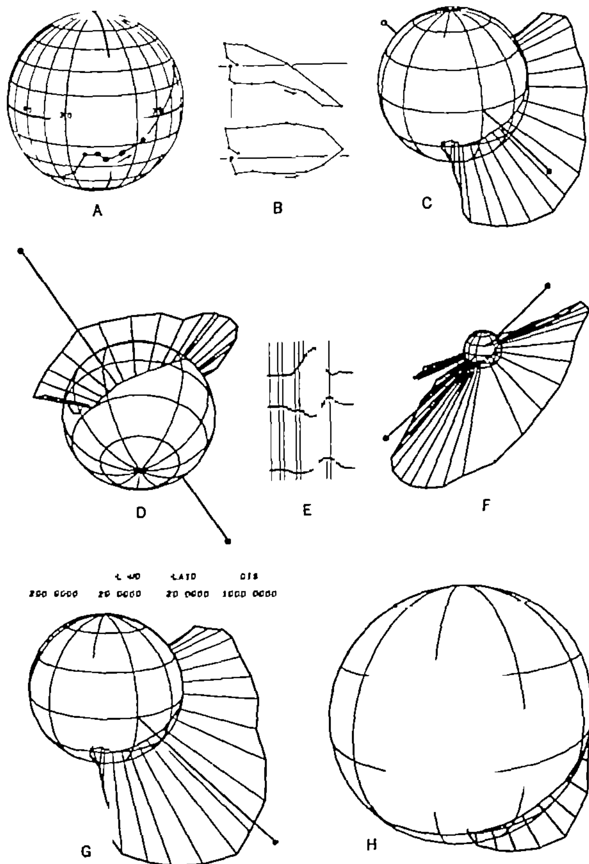


Fig 1

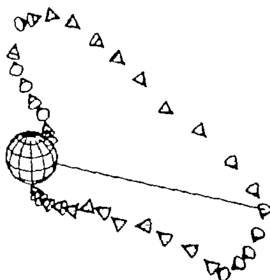


Fig 2

perspectiv We are experimenting with other means by hich the front and back and the upper nd lower halves of the sphere may be distinguished t glance. The radius is 200 units the observer distance 3 000 units. The observer axis is 20° −20° (longitude latitude). The units are those of the SC 4020, hich carries a range of 0 to 99 000,000 nits. The magnitude of the maximum ector is 505 units and, as ts value in microvolts is 1 111 one unit of the SC 4020 is equivalent in this instance to 2 2 microvolts of ector magnitude

I Fig 1 D the observer is below and behind the loop. The observer is is −25° 45° and the observer distance is 3,000 units

I these displa the sphere remains fixed and the Y axis ertical It is the observer who moves The observer axis an be recognized in each iew as it is that poi hich lies a the en er of he ircumference It is 11 −11 for example in Fig 1 I

I Fig 1 F he observer b nd behind be maximum ec or His is −20 −2° and his distance 3,000 its The adius of he sphere is programmed equ I 10 per cen of he ma imum ector The returning limb of the QRS loop descends the fa of he ontracted phere ... south exter cou se en er −25 −30° nd emerges the T loop It is amusing hink that, if the T segmen ere more prominen this subjec ould mpleted tra erse he sphere and po he nd of the QR the I The position nd ... each segmen nd the adius of he ph b ... ha ... linical ... the

Fig 1 G is ncluded demonst he effec of decreasing the observer distance 1 1 000 to as opposed the 3 000 of Fig 1 E The adius nd he observer of bo h gures are identical The al er m grid and loop onse quenc of the observer relativ proximity to the display A portion of the titling that accompa ies each frame is how bove the figure It states that the radius I 700 the observer xis is 20° −20° and the observer distance is 1,000.

Most of the loop lies ithi the sphere of Fig 1 H This is an early untitled attempt and all w know is that the observer axis is 20° −20° The curv ture of the grid and the limited horizon how ever indicat that the observer is fairly close to the phere.

Except for the equipment described abov there is no intervention between the subject and the finished display Many subjects can be recorded on the same tape and their displays can be photographed in sequence on single roll of paper Each picture is completed in less than 2 seconds which is the time required for it frame t move I t position.

Motion pict res of the dev loping loop are made on 35 mm film by synchronizing the motion pi ture camera nd the instantaneous ectors. One frame is advanced for each ector displayed. T enty three f ames per second ha been programmed, and i this instance, the loop completes it course in about 2 seconds of screen time The still and motion picture cameras operat simultaneousl nless the program calls for one to be turned off Such motion pictures are being produced.

Variations may be introduced. Directional arrow heads are being programmed onto the loop The ector shafts can be erased. The sphere can be made transparent. The observer can go inside the sphere and examine the busy area about its center The intersecting, cardinal planes may be chosen as a frame of reference. The loop may be centered within cube and joined by perpendiculars to its projec tions on 3 faces. It may be simulated by an inter rupted ribbon, as in an old illustration of ours. It may be displayed by sequence of small, right conic figures with contrasting inner and outer surfaces nd as ad ancing base When these are draw to perspecti and their longitudinal axes adjusted to the curvature of the loop their ttitudes and positions with respect t each other and to the null point will offer 3 dimensional display with or ithout the spherical frame of reference. This is being programmed

An example is show in Fig 2 in wh h the observer axis is 90° 30° and in which all of the shaf but that of the maximum vector ha been ... nated.

I sh to thank Digital Programming Services Incorporated of Boston, Mass The Avco Corpor tion Computer Center of Wilmington Mass and M Harry Glenn Cooper of the Stromberg Carlson Corporation.

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Notes on teaching: How some words prevent learning

Certain ords ma t nd in th w y of learning For example the left trium is ot on the left It is a posterior truct re nd is located between the spine nd the rema nder of the heart n th central portion of the rdiac ilhouette. The term left trium lmost forces one t belie that the tru t re ought t be on the left. When one realizes her the left atri m is really located then it is eas nderstand hy mitral regurgitation may a se the trium t expand and "kick the re mainder of the heart anteriorly because the im movable pine limits the movement posteriorly Thus ca see lift of the anterior chest that can often be palpated When one really know where the trium is located then one can nderstand why certai murmurs d to mitral regurgit tion may be heard in the back or in the second right inter space near the sternum thereby simulating ortic stenosis.

The right entricle is located more nteriorly than t is on the right As long as one has the mental mage that the "right ventricle is really on the right it may be difficult to understand why hyper trophy of the structure produces an anterior lift of th chest

There are many such words that tand in the way of learning These two examples illustrate how certain anatomic labels—historically correct but anatomically incorrect—prevent nderstanding

W should teach just where the left atrium a nd the right entricle are located.

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